VISIT…

DRUGS AND THE PHARMACEUTICAL SCIENCES

Volume 129

GENERIC DRUG PRODUCT DEVELOPMENT

Solid Oral Dosage Forms

Second Edition

Edited by

Leon Shargel

Isadore Kanfer

CRC Press
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Generic Drug
Product Development

Solid Oral Dosage Forms

Second Edition

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Generic Drug Product Development

Solid Oral Dosage Forms

Second Edition

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Preface

Since the publication of the first edition of this book, the generic pharmaceutical industry has greatly expanded and has become more competitive. Many generic drug companies have merged, forming large global companies that also manufacture branded drug products. New generic pharmaceutical companies have entered into the marketplace increasing competition. To be successful, generic drug products must be manufactured in a cost-effective manner and on a timely basis. The manufacturer who is first to file a new generic drug product may reap a high financial reward. Even with the successful development of an approvable generic drug product, the manufacturer has financial risks due to possible patent infringement and other legal challenges.

With the expansion of the generic pharmaceutical industry, new approaches have been developed for the manufacture of generic drug products, including the demonstration of drug product performance and meeting regulatory/legal requirements for market approval. Besides patents, costs, and time issues, the manufacturers of generic drug products must develop a product that is a pharmaceutical equivalent and bioequivalent to the reference listed product (usually the brand product) and ensure that the product meets various drug product performance standards such as good manufacturing practices and bioequivalence and also regulatory guidelines. Once approved by the regulatory agency (e.g., FDA), it is assumed that the generic drug product will have the same therapeutic safety, efficacy, and clinical performance as its brand-name counterpart.

This second edition updates each of the previous chapters and includes a new chapter on the US Pharmacopoeia and Pharmacopeia Harmonization. The objectives of this edition are similar to those of the first edition of *Generic Drug Product Development—Solid Oral Dosage Form*. The objectives are to describe, from concept to market approval, the development of high-quality, safe, and efficacious solid oral generic drug products. The revised edition provides a comprehensive account of the scientific, regulatory, and legal considerations for the development of generic drug products from project initiation incorporating the more recent concept of "Quality by Design" to marketing approval. As in the previous edition, the emphasis of this book is the development of solid oral generic drug products. However, much of the material contained in this textbook will have application to the development of other generic drug products.

The audience for this book is the members of the pharmaceutical industry, academia, and health practitioners who are interested in generic drug development and need more information concerning drug product initiation, drug product formulation, biopharmaceutics, drug delivery, bioequivalence, regulatory, and legislative issues. As in the previous edition, emphasis is on practical information for the development of a generic drug product. The text assumes that the reader has basic knowledge of pharmaceuticals and is interested in generic drug product manufacture.

Although the contents of the book emphasize the development of oral generic drug products for the FDA regulatory approval process, much of the information is applicable to other generic pharmaceutical products and approval by other regulatory agencies.

Editors

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1 Generic Drug Product Development and Therapeutic Equivalence

Leon Shargel and Isadore Kanfer

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THERAPEUTIC EQUIVALENCE AND GENERIC DRUG PRODUCTS

Multisource drug products are drug products that are marketed by more than one manufacturer, contain the same active pharmaceutical ingredient (API) or drug substance, in the same dosage form, and are given by the same route of administration. Multisource drug products contain identical drug substances and may meet compendial (e.g., United States Pharmacopeia [USP]-National Formulary monograph) standards of strength, quality, purity, and identity. However, multisource drug products should not be considered automatically as interchangeable or therapeutic equivalent, generic drug products. The term "generic product" has somewhat different meanings in different jurisdictions [1]. Regulatory approval for interchangeable multisource products may differ somewhat in each country. To be considered as an interchangeable generic drug product, the product must be approved by the relevant regulatory agency as a therapeutic equivalent. A therapeutic equivalent, generic drug product must have the same performance characteristics and is expected to have the same clinical effect and safety profile as the reference product when administered to patients under the conditions specified in the labeling. Because the reference product (generally the brand's or innovator's product) sold in different countries may not be bioequivalent to each other, each domestic market has regulations that decide which reference product should be used during generic drug product development and approval. International regulatory requirements for generic drug products are discussed in another book in this series [2].

Pharmaceutical Equivalents and Pharmaceutical Alternatives

Pharmaceutical equivalents are drug products that contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5 mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring, configuration, release mechanisms, packaging, excipients (including colors, flavors, and preservatives), expiration time, and, within certain limits, labeling [3]. Pharmaceutical alternatives are drug products that contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250 mg capsules vs. tetracycline phosphate complex, 250 mg capsules; quinidine sulfate, 200 mg tablets vs. quinidine sulfate, 200 mg capsules) [3]. The U.S. Food and Drug Administration (FDA) considers tablets and capsules as pharmaceutical alternatives even if the same API in each is bioequivalent. Other countries may accept bioequivalent capsules and capsules of the same drug as interchangeable drug products. Pharmaceutical alternatives may also be different dosage forms and strengths within a product line by a single manufacturer such as extended-release products compared with immediate-release or standard-release formulations of the same active ingredient [3].

Therapeutic Equivalence

In the United States, a therapeutically equivalent drug product must meet certain FDA criteria [3,4], which are as follows:

- Approved as safe and effective
- Pharmaceutical equivalent
  - Contain identical amounts of the same active drug ingredient in the same dosage form and route of administration
  - Meet compendial or other applicable standards of strength, quality, purity, and identity
- Bioequivalent
  - Do not present a known or potential bioequivalence problem
  - Meet an acceptable in vitro standard, or if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard
- Adequately labeled
- Manufactured in compliance with current good manufacturing practice regulations

Economic Savings

Generic drug products are typically sold at substantial discounts from their brand name counterparts. The Generic Pharmaceutical Association (GPhA) recently released an independently conducted analysis showing that the savings to consumers and the U.S. health care system from the use of generic prescription drugs rose to a current rate of $1 billion every other day, totaling $193 billion in 2011 and $1.07 trillion over the last 10 years (2002–2011) [5]. The report also revealed that savings from the use of generic drug products in 2011 increased 22% over the prior year, marking the largest year-over-year increase since 1998, and 10% higher than the 10-year average.

Savings from newer generic medicines that have entered the market since 2002 continue to increase exponentially, totaling $481 billion over the past 10 years. In 2011, approximately 80% of the 4 billion prescriptions written in the United States were dispensed using generic medicines, while accounting for only 27% of the total drug spending. The study also predicts that future savings to be achieved through generic prescription medicines will climb at an ever-increasing annual rate. Consumers chose the generic alternative 94% of the time in 2011 and this is a clear indication of the quality, safety, and efficacy of the FDA-approved generic products.

THERAPEUTIC EQUIVALENCE, DRUG PRODUCT QUALITY, AND DRUG PRODUCT PERFORMANCE

Drug product performance, in vivo, may be defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance [6]. Bioavailability is defined as the rate and extent to which the active ingredient or

active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action [3]. Thus, drug product performance applies to both locally acting drug products, such as topical corticosteroids, and drugs intended for systemic absorption. The performance of each drug product must be consistent and predictable to assure both clinical efficacy and safety.

Defects in product quality can lead to poor drug product performance and affect safety and/or efficacy. Each component of the drug product and the method of manufacture contribute to quality. Quality is maintained by implementing systems and procedures that are followed during the development and manufacture of the drug product. Bioavailability, bioequivalence, and drug release/dissolution are important measures of drug product performance. Equivalent drug product performance is necessary to assure therapeutic equivalence. Thus, manufacturers of new and generic drug products must take into consideration drug product quality and drug product performance, so that each manufactured batch is equivalent and performs similarly in vivo. Likewise, both the generic drug product and its brand name alternative must also perform similarly, which is the basis of therapeutic equivalence.

GENERIC DRUG PRODUCT DEVELOPMENT

Generic drug product development uses a different approach and strategy compared with that used to develop a brand name drug product containing a new chemical entity. Generic drug product manufacturers must formulate a drug product that will have the same therapeutic efficacy, safety, and performance characteristics as its brand name counterpart. To gain market approval, a generic drug product cannot be "superior" or "better" than the brand name drug product. The key factor is that the generic drug product should meet all the necessary criteria to be therapeutically equivalent to the brand name (reference) drug product.

The manufacturer of a generic drug product has certain constraints in formulation development that differ from the formulation development of a brand name drug product. Generic drug manufacturers also face a variety of legal challenges from the brand name (innovator) pharmaceutical industry. For example, a generic drug manufacturer may not be able to use the same or similar inactive ingredients or excipients as in the brand formulation due to existing patents by the innovator. These issues will be discussed more thoroughly in subsequent chapters.

Initially, the generic manufacturer must find a source of the API and develop a finished dosage form (Figure 1.1). The method of manufacture of the API and its physical chemical characteristics, such as polymorphic (crystalline) form, should not infringe with patents filed by the innovator. In addition, an impurity profile for the generic API may be different from the brand due to a different synthetic routes of manufacture. The finished dosage form (e.g., an immediate-release or modified-release tablet) must also not infringe on formulation patents. To avoid patent infringement, the dosage form manufactured by the generic drug product manufacturer may use a different drug release mechanism compared with the brand; therefore, the

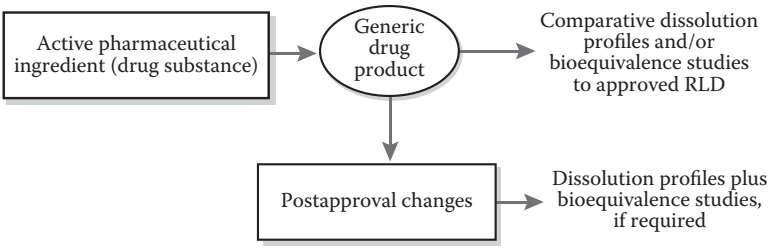
Active pharmaceutical ingredient (drug substance)
Generic drug product
Comparative dissolution profiles and/or bioequivalence studies to approved RLD
Postapproval changes
Dissolution profiles plus bioequivalence studies, if required

FIGURE 1.1 Drug product performance and generic drug product development. Reference listed drug (RLD) product performance may be determined in vivo by bioequivalence studies or in vitro by comparative drug/release dissolution studies. (From Shargel, L. et al. *Applied Biopharmaceutics & Pharmacokinetics*, 6th edition. McGraw-Hill, New York, 2012, Chapter 15.)

relationship between drug release and bioavailability may not be predictable in vitro. After drug approval, any scale-up, post-approval changes, including a site change, may also require comparative bioavailability studies to confirm bioequivalence.

SELECTION OF A GENERIC DRUG PRODUCT FOR MANUFACTURE

The main driving force for the selection of generic drug products for manufacture is the estimated sales volume for the branded product and the potential market share that the firm expects to have once the generic drug product is manufactured and approved for marketing (Table 1.1). Patent and legal considerations are also very important and are discussed more fully in Chapter 15. The generic drug manufacturer must consider the expiration date of the patent for the active ingredient and any other patent claims and exclusivities that the innovator firm has filed. In addition, the generic drug manufacturer needs to consider the lead time that is needed to make the product and submission of an Abbreviated New Drug Application (ANDA) to the FDA for approval. Timing is important, because the generic manufacturer would like to have their product submitted and approved just before patent expiration of the innovator's drug product. There is a large financial incentive to being the first generic drug product filed and approved by the FDA. The Hatch–Waxman Act, as

TABLE 1.1
Considerations in the Selection of a Generic Drug Product for Manufacture

Sales and potential market share
Patent expiration and exclusivity issues
Availability of API
Timing
Available technology
Formulation and dosage form
Experience
Development costs

explained below, provides a 180-day exclusivity, under certain conditions, for the generic manufacturer who is first to file.

The availability of technology and the cost of acquiring technology to manufacture the product will also impact the choice of generic drug product. For example, the proposed generic drug product might require special manufacturing equipment, a sterile environment, specialized packaging, or other expensive items. The firm must then consider whether this equipment, technology, and/or expertise are available in-house or must be acquired. Formulation considerations include the availability of raw materials, chemical purity, polymorphic form, and particle size of the API and any patents that the innovator company has filed, including patents for the synthesis of the API and composition of the dosage form. Experience with certain drug products will also affect the choice of generic drug product development. For example, some generic drug manufacturers may make a wide variety of dosage forms as well as solid and liquid oral dosage forms, including immediate-release and modified-release products as well as topical drug products (ointments and creams). Other generic firms may make specialty drug products such as transdermal, inhalation, or sterile drug products. Niche drug products, such as transdermal drug products, ophthalmic products, and others, may be difficult to make and also riskier but may have a greater financial reward due to less competition from other generic drug firms.

The decision to proceed with the development of a generic drug product should therefore be based on well-researched data that primarily indicate market value together with a sound knowledge of patent expiry dates, predicted market share, and growth rate for the product, among others. Government spending trends on medicines, which, in some countries, may be in the region of 40% or even more of the total market, should not be overlooked. The predicted profitability of the new generic product will require strategic planning for the subsequent launch timing, which must take into account the expected generic price and knowledge of anticipated competitors, such as who they are and when they are expected.

LEGISLATIVE AND REGULATORY ISSUES

The FDA was established in 1906 by the Federal Food, Drug, and Cosmetic Act (the Wiley Act) to prevent the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, among others [7]. In 1938, the Act was amended to require drug manufacturers to file a New Drug Application (NDA) for each newly introduced drug product and to provide data to establish the safety of the drug product. In 1962, the Kefauver–Harris Amendments to the Act required all drug manufacturers to establish that their products were effective for their claimed indication(s), in addition to adhering to the safety requirements. Consequently, the FDA contracted with the National Academy of Sciences/National Research Council in 1968 to evaluate those drugs first introduced between 1938 and 1962 for effectiveness. This review program was called the Drug Efficacy Study Implementation (DESI) review, and drugs for which effectiveness was determined through the DESI review could be marketed with approval of an NDA. For drugs approved through the DESI review

process, manufacturers of brand name products submitted data as a supplement to the existing NDAs, confirming the safety and effectiveness of their products. During the implementation of the DESI review program, more than 3400 products and related generics were reviewed and approximately 900 drug products were removed from the market. Many other products were reformulated or relabeled to limit their uses to selected indications only. One effect of the DESI study was the development of the abbreviated new drug application (ANDA) in 1970 for reviewed marketed products that required changes in existing labeling to be in compliance. However, manufacturers of any new drug product (brand name or generic) marketed after 1962 were required to prove both the safety and the efficacy of such products. The 1962 legislation provided an exemption from the NDA approval process for drugs that had been marketed before 1938, based on the assumption that they were generally recognized as safe and effective—the so-called "grandfather" provision. Manufacturers continued to conduct clinical efficacy and safety studies until 1978, when a dispensation was granted to manufacturers whereby the citation of published reports of trials documenting safety and efficacy would suffice.

In 1984, the Drug Price Competition and Patent Term Restoration Act (Hatch–Waxman Act) extended the ANDA process to generic versions of drugs marketed after 1962 (Table 1.2). This Act eliminated the requirement that generic drug manufacturers duplicate expensive, time-consuming clinical and nonclinical studies to demonstrate safety and efficacy. Furthermore, this Act expedites the availability of generic drug products provided that the generic drug manufacturer shows that no patent infringement would occur. The Hatch–Waxman Act also compensated the innovator drug manufacturer for perceived losses due to competition from the generic drug products by extending the patent terms of some brand name drug products for up to an additional 5 years to make up for time lost while their products were going through the FDA's approval process.

The Drug Price Competition and Patent Term Restoration Act was subsequently amended to make provision for a pharmaceutical manufacturer (sponsor) to seek approval from the FDA to market a generic drug product before the expiration of a patent relating to the brand name drug upon which the generic is based. This amendment, known as the "Bolar amendment," allowed the ANDA approval process to begin before the patent on the brand name drug expired. As part of the ANDA submission, the sponsor must consider the pertinent patents and provide a "certification" that, in the opinion of the sponsor and to the best of the sponsor's knowledge

TABLE 1.2
Drug Price Competition and Term Restoration Act of 1984 (Hatch–Waxman Act)

Created a framework for patent term extensions and nonpatent exclusivity periods for brand name drug products
Established for the first time an ANDA approval process specifically for generic manufacturers
Provided for pre-patent expiration testing (Bolar provision) and generic drug product exclusivity

with respect to each patent that claims the listed drug, the patent is invalid or is not infringed by the generic product.

The current FDA Federal Food, Drug, and Cosmetic Act, with its subsequent amendments, is the basic food and drug law of the United States and is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging are truthful, informative, and not deceptive. The mission of the FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook.

The Federal Register publishes a daily record of proposed rules, final rules, meeting notices, etc. (http://www.access.gpo.gov/). The final regulations are collected in the Code of Federal Regulations, or CFR (http://www.access.gpo.gov/). The CFR is divided into 50 titles representing broad areas subject to Federal regulations. The FDA's portion of the CFR interprets the Federal Food, Drug, and Cosmetic Act and related statutes. Title 21 of the CFR contains most of the regulations pertaining to food and drugs. The regulations document most actions of all drug sponsors that are required under Federal law.

Generic Drug User Fee Amendments of 2012

The generic drug industry has been very successful and has expanded globally. The volume of applications to the FDA has posed significant regulatory challenges and is straining limited public resources. With the increased volume of new generic drug applications, the time required for scientific review and inspections has lengthened along with a backlog of pending generic applications. Generic Drug User Fee Amendment of 2012 (GDUFA) is designed to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry [8]. GDUFA aims to put the FDA's generic drug program on a firm financial footing and ensure timely access to safe, high-quality, affordable generic drugs. GDUFA enables the FDA to assess user fees to fund critical and measurable enhancements to the performance of the FDA's generic drugs program, bringing greater predictability and timeliness to the review of generic drug applications.

GENERIC DRUG APPROVAL

The FDA's Office of Generic Drugs (OGD) is responsible for reviewing the ANDA and approving the drug product for marketing. The FDA's OGD has a website (http://www.fda.gov/cder/ogd/) that provides additional information for manufacturers of generic drug products that include an interactive flow chart presentation of the ANDA review process (Figure 1.2) and describes how the FDA determines the quality, safety, and efficacy of generic drug products before approval for marketing. Generic drug application reviewers focus on bioequivalence data, chemistry and manufacture, quality, microbiology data where relevant, requests for plant inspection, and drug labeling information. The FDA website is designed for individuals from pharmaceutical companies, government agencies, academic institutions, private

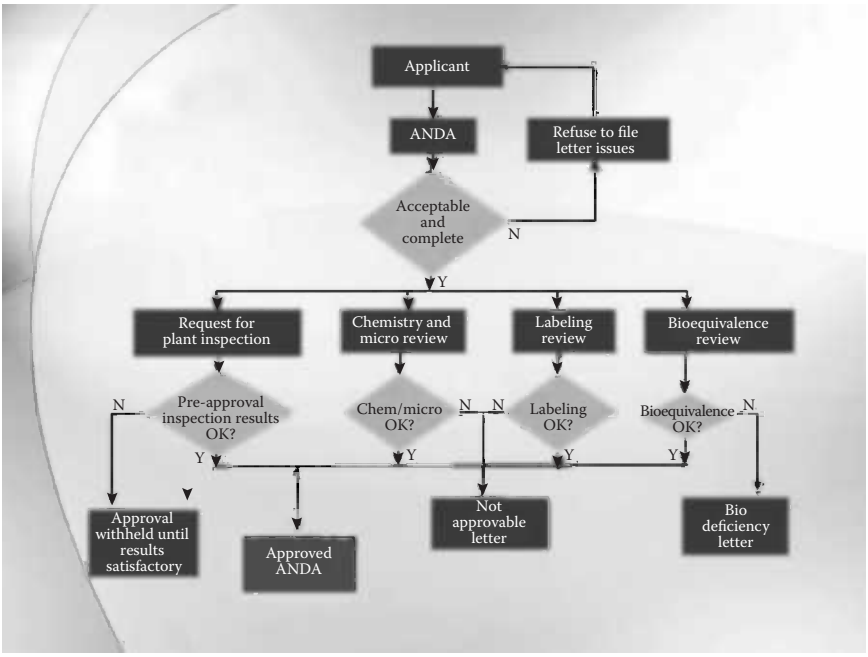

FIGURE 1.2 Generic drug review process.

organizations, or other organizations interested in bringing a generic drug product to market. Details of the FDA review and approval process are discussed in Chapter 9.

The ANDA is based on bioequivalence to the brand name product, appropriate chemistry and manufacturing information, and appropriate labeling. Generic drug sponsors do not have to duplicate the nonclinical animal toxicity studies or expensive clinical efficacy and safety studies that are included in the NDA, which is submitted to the FDA for market approval of the brand name drug product. The ANDA contains data, which, when submitted to the FDA's Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD), provide for the review and ultimate approval for marketing a generic drug product.

FDA-approved generic drugs must meet the same rigid standards as the innovator drug. To obtain FDA approval, a generic drug product must

- Contain the same active ingredients as an approved "RLD product" (generally, the innovator drug—the inactive ingredients may vary)
- Be identical in strength, dosage form, and route of administration
- Have the same use indications
- Be bioequivalent
- Meet the same batch requirements for identity, strength, purity, and quality
- Be manufactured under the same strict standards of the FDA's good manufacturing practice regulations as required for innovator products

An FDA-approved generic drug product is considered a therapeutic equivalent to the innovator or brand name drug product in terms of quality and performance characteristics and is expected to have the same safety and efficacy. An ANDA checklist for completeness and acceptability of an application is available on the FDA website (http://www.fda.gov/cder/ogd/anda_checklist.doc).

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

The FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) lists all approved products, both innovator and generic, approved based on safety and effectiveness by the FDA [3]. The Orange Book is available on the Internet (http://www.fda.gov/cder/ob/default.htm) and is updated monthly. The list contains therapeutic equivalence evaluations for approved multisource prescription drug products. Therapeutic equivalence or inequivalence for prescription products is determined based on the therapeutic equivalence codes provided within that specific dosage form (Table 1.3). The coding system for therapeutic equivalence evaluations is constructed to allow users to determine quickly whether the FDA has

TABLE 1.3
Therapeutic Equivalence Evaluations Codes (Orange Book)

A	Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products. "A" products are those for which actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence
AA	Drug products in conventional dosage forms not presenting bioequivalence problems
AB	Drug products meeting necessary bioequivalence requirements
AN	Solutions and powders for aerosolization
AO	Injectable oil solutions
AP	Injectable aqueous solutions and, in certain cases, intravenous nonaqueous solutions
AT	Topical products
B	Drug products that the FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products
B*	Drug products requiring further FDA investigation and review to determine therapeutic equivalence
BC	Extended-release dosage forms (capsules, injectables, and tablets)
BD	Active ingredients and dosage forms with documented bioequivalence problems
BE	Delayed-release oral dosage forms
BN	Products in aerosol-nebulizer drug delivery systems
BP	Active ingredients and dosage forms with potential bioequivalence problems
BR	Suppositories or enemas that deliver drugs for systemic absorption
BS	Products associated with drug standard deficiencies
BT	Topical drug products with bioequivalence issues
BX	Drug products for which the data are insufficient to determine therapeutic equivalence

evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information based on the FDA's evaluations (second letter).

Reference Listed Drug

In most countries, the RLD is generally the innovator drug product ("Brand"), which is marketed based on a full dossier that includes chemical, biological, safety, clinical efficacy, labeling, etc. The FDA identifies the RLD to which the in vivo bioequivalence (reference standard) and, in some instances, the in vitro bioequivalence of the applicant's product are compared (Table 1.4). By designating a single RLD as the standard to which all generic versions must be shown to be bioequivalent, the FDA hopes to avoid possible significant variations among generic drug products and their brand name counterparts. Such variations could result if generic drug products were compared with different RLDs.

At times, there may be two different NDA holders for the same active ingredient. In Table 1.4, Adalat CC (nifedipine ER tablet) is an RLD listed as AB1 and Procardia XL (nifedipine ER tablet) is an RLD listed as AB2. Because Adalat CC and Procardia XL have not established bioequivalence to each other, the ANDA sponsor must consider which RLD will be used. In the case of other domestic market places, such as European countries, the RLD is usually the brand name that has been approved and marketed domestically in that country.

TABLE 1.4
RLD—Nifedipine Extended-Release Oral Tablet

TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
AB1	Yes	Nifedipine tablet	Extended release; oral	90 mg	Adalat CC	Bayer Healthcare
AB1	No	Nifedipine tablet	Extended release; oral	90 mg	Nifedipine	Actavis
AB1	No	Nifedipine tablet	Extended release; oral	90 mg	Nifedipine	Valeant International
AB2	Yes	Nifedipine tablet	Extended release; oral	90 mg	Procardia XL	Pfizer
AB2	No	Nifedipine tablet	Extended release; oral	90 mg	Nifedipine	Mylan
AB2	No	Nifedipine tablet	Extended release; oral	90 mg	Nifedipine	Osmotica Pharm
AB1	No	Nifedipine tablet	Extended release; oral	90 mg	Nifedipine	Mylan

Source: Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (www.accessdata.fda.gov/scripts/cder/ob/default.cfm.)

PATENTS

New drugs, like most other new products, are developed under patent protection. The patent protects the investment in the drug's development by giving the company the sole right to sell the drug while the patent is in effect. Patents are granted by the U.S. Patent and Trademark Office anytime in the "life" of the drug. A patent expires 20 years from the date of filing. When patents or other periods of exclusivity expire, manufacturers can apply to the FDA to sell generic versions.

The Orange Book provides patent and exclusivity information in an Addendum. This Addendum identifies drugs that qualify under the Drug Price Competition and Patent Term Restoration Act (1984 Amendments) for periods of exclusivity, during which ANDAs and applications described in Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for those drug products may, in some instances, not be submitted or made effective, and provides patent information concerning the listed drug products. Those drugs that have qualified for Orphan Drug Exclusivity pursuant to Section 527 of the Act and those drugs that have qualified for Pediatric Exclusivity pursuant to Section 505A are also included in this Addendum.

Exclusivity prevents the submission or effective approval of ANDAs or applications described in Section 505(b)(2) of the Act.

Patents that are listed in the Orange Book include

- Patents that claim the active ingredients or ingredients
- Drug product patents that include formulation/composition patents
- Use patents for a particular approved indication or method of using the product

The Bolar amendment to the Drug Price Competition and Patent Term Restoration Act allows a pharmaceutical manufacturer (sponsor) to seek approval from the FDA to market a generic drug product before the expiration of a patent relating to the brand name drug product upon which the generic is based. As part of the ANDA, the sponsor must consider the pertinent patents and provide the results to the FDA. The Act requires patent information to be filed with all newly submitted Section 505 drug applications and that no NDA may be approved after September 24, 1984, without the submission of pertinent patent information to the FDA. The ANDA sponsor must provide a "certification" that, in the opinion of the sponsor and to the best of the sponsor's knowledge with respect to each patent that claims the listed drug, some or all of the following certification may be submitted:

Paragraph I: That such patent information has not been filed
Paragraph II: That such patent has expired
Paragraph III: Of the date on which such patent will expire
Paragraph IV: That such patent is invalid or will not be infringed on by the manufacture, use, or sale of the new drug for which the application is submitted

A certification under Paragraph I or II permits the ANDA to be approved immediately, if it is otherwise eligible. A certification under Paragraph III indicates that the ANDA may be approved on the patent expiration date.

If the Orange Book lists one or more unexpired patents, the sponsor of the ANDA who seeks effective approval before the patent's expiration must either

- Challenge the listing of the patent (e.g., file a Paragraph IV certification that the patent is invalid or will not be infringed on by the manufacture, use, or sale of the drug product)
- File a statement that the application for use is not claimed in the listed patent

Exclusivity

The generic applicant must notify the patent holder of the submission of the ANDA. Because the patent holder can immediately sue the first generic sponsor company who submits an ANDA with a Paragraph IV statement, a 180-day period of market exclusivity is provided to that generic applicant. This special dispensation is considered as a reward to the generic manufacturer who took a risk in challenging the patent. If the patent holder files an infringement suit against the generic applicant within 45 days of the ANDA notification, an FDA approval to market the generic drug product is automatically postponed for 30 months, unless, before that time, the patent expires or is judged to be invalid or not infringed upon. This 30-month postponement gives the patent holder time to assert its patent rights in court before a generic competitor is permitted to enter the market. Only an application containing a Paragraph IV certification may be eligible for exclusivity, and to earn the period of exclusivity, the ANDA applicant must be sued by the patent holder and successfully defend the suit (see Chapter 15 for more details).

Under certain circumstances, the patent holder may obtain exclusivity for a branded drug product that essentially extends the time on the market without competition from the generic drug product. Exclusivity works similar to patents and is granted by the FDA if statutory provisions are met. Types of exclusivity are listed in Table 1.5.

TABLE 1.5
Types of Exclusivity

Exclusivity	Time for Exclusivity	Exclusivity Criteria
Orphan drug exclusivity (ODE)	7 years	Upon approval of designated orphan drug, the Office of Orphan Products issues letter when exclusivity granted—separate from other types of exclusivity
New chemical entity (NCE)	5 years	Upon first time approval of new chemical entity
"Other" exclusivity	3 years for a "significant change" if criteria are met	For certain "significant changes" approved on an NDA or supplement if new clinical studies essential for approval, conducted or sponsored by applicant, have been done "Changes" may include (but are not limited to) new ester/salt, new dosage form, new route, new indication, new strength, and new dosing schedule
Pediatric exclusivity (PED)	6 months added to existing patents or exclusivity	A period of 6 months' exclusivity is added to any existing exclusivity or patents on all applications held by the sponsor so that active moiety pediatric exclusivity does not stand alone

RESOURCES FOR ANDA SUBMISSIONS

The FDA's CDER (http://www.fda.gov/cder) and the OGD (http://www.fda.gov/cder/ogd/) provide assistance to the sponsor of an ANDA to meet the legal and regulatory requirements of an application. FDA provides assistance through its website and publications, guidances, internal ANDA review principles, policies, and procedures. A few resources for ANDA and NDA drug product development are listed in Table 1.6.

Guidance Documents for ANDAs

Guidance documents represent the Agency's current thinking on a particular subject (http://www.fda.gov/cder/regulatory/default.htm). These documents are prepared for the FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and to establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such an approach satisfies the requirements of the applicable statute, regulations, or both. The FDA has numerous guidances for industry that relate to ANDA content and format issues [9].

Manual of Policies and Procedures

Manuals of Policies and Procedures (MaPPs) provide official instructions for internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities, both internal and external [10]. MaPPs define external activities as well. All MaPPs are available for the public to review to get a

TABLE 1.6
Selected FDA Resources for New (NDA) and Generic (ANDA) Drug Product Development

Adverse event reporting system (AERS)
Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)
Bioequivalence recommendations for specific products
Bioresearch monitoring information system
Clinical investigator inspection list
Dissolution methods database
Drug establishment's current registration site
Drugs @ FDA Database
Inactive ingredient search for approved drug products
National drug code directory
Postmarket requirements and commitments
Approvals

better understanding of office policies, definitions, staff responsibilities, and procedures. MaPP documents to help prepare ANDAs are listed together on the CDER's Manual of Policies and Procedures Web page (http://www.fda.gov/cder/mapp.htm).

Freedom of Information

The 1996 amendments to the Freedom of Information Act (FOIA) mandate publicly accessible "electronic reading rooms" with the FDA FOIA response materials and other information routinely available to the public with electronic search and indexing features. Before submitting an FOIA request, the sponsor should check to see if the information is already available on the FDA's website (http://www.fda.gov/foi/foia2.htm). There is a search engine to help find information [11].

Additional Resources Regarding Drug Development

The FDA provides additional resources regarding drug development on its website (http://www.fda.gov/cder/ode4/preind/Gen_Additional_Resources.htm). These resources are summarized in Table 1.7.

Drug Master File

The Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drug substances. The submission of a DMF is not required by law or FDA regulation. Further information regarding DMFs is available in the CDER Guidance Document on Drug Master Files or 21 CFR 314.420 [12].

TABLE 1.7
General Information Regarding Drug Development

General FDA Information
Resources within FDA
External Resources—General
External Resources—Education
Review Jurisdiction of Drug Product Classes within ODE IV
Items of General Interest
CDER Guidance Documents/MaPPs
Federal Register
CFR Title 21
FDA Forms Distribution Page
International Conference on Harmonisation Documents
IND/NDA Jackets/Submission Covers
DMF Information

United States Pharmacopeia

The USP (http://www.usp.org) promotes public health by establishing and disseminating officially recognized standards of quality and authoritative information for the use of medicines and other health care technologies by health professionals, patients, and consumers. USP works closely with the FDA, the pharmaceutical industry, and the health professions to establish authoritative drug standards. These standards are enforceable by the FDA and the governments of more than 35 other countries and are recognized worldwide as a hallmark of quality. More than 3700 standard monographs are published in the USP and the National Formulary, the official drug standards compendia. USP also provides more chemical reference standards to carry out the tests specified in USP-National Formulary [13].

International Conference on Harmonisation

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is composed of the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration (http://www.ifpma.org/ich1.html).

The purpose of the International Conference on Harmonisation is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonization is a more economical use of human, animal, and material resources and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health [14].

BIOTECHNOLOGY-DERIVED DRUG PRODUCTS (BIOSIMILARS)

Biotechnology-derived drugs (biologics and biopharmaceuticals), in contrast to drugs that are chemically synthesized, are derived from living sources such as humans, animals, or microorganisms. Many biologics are complex mixtures that are not easily identified or characterized and are manufactured using biotechnology or are purified from natural sources. Other biological drugs, such as insulin and growth hormone, are proteins derived by biotechnology and have been well characterized. In recent years, there have been various discussions whether a generic biotechnology-derived drug product can be developed and be considered both bioequivalent and interchangeable to the brand alternative. Issues have included the ability to fully characterize the active ingredient(s), that immunogenicity-related impurities may be present in the product, and that the manufacture of a biological drug product is process dependent.

The FDA Patient Protection and Affordable Care Act (Affordable Care Act) of March 23, 2010, amends the Public Health Service Act or PHS Act to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product [15]. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act. Under the Biologics Price Competition and Innovation Act, a biological product may be demonstrated to be "biosimilar" if data show that, among other things, the product is "highly similar" to an already approved biological product. FDA biosimilars are products that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM292463.pdf).

The FDA is using a stepwise approach to demonstrate biosimilarity that can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, clinical immunogenicity, and clinical safety and effectiveness. As such, the FDA will consider the totality of the evidence to review applications for biosimilar products. Although biosimilar drug products are currently being developed and a few have been approved, this book only focuses on the development of therapeutic equivalent, generic drug products containing well-characterized, smaller molecules.

SUMMARY

The market for generic drug products continues to increase with the expiration of patents and exclusivities for major brand name drug products and to the demand by consumers and governments for less expensive generic alternatives. From a scientific perspective, generic drug product manufacturers must formulate a drug product that will have the same quality, therapeutic efficacy, safety, and performance as its brand name counterpart. Formulation development of an innovator drug product has minimal constraints with respect to choice of excipients, manufacturing methods, and performance characteristics. In contrast, generic drug manufacturers must demonstrate that their formulation is a pharmaceutical equivalent, is bioequivalent, and has the same quality and performance characteristics as the brand name counterpart. Moreover, the generic drug manufacturer will continue to face a variety of legal, regulatory, and patent challenges from the brand name pharmaceutical industry that may delay the entry of the generic drug in the marketplace. The availability of generic drug products will, nevertheless, continue to play an important role, both nationally and internationally, by providing cost-effective medicines to the wider public, which will bring great benefits to consumers as well as to health authorities in nations around the world in their quest to make medicines more available and affordable. The quest for biotechnology-derived drugs and the manufacture of biosimilar drug products will also expand. However, biotechnology-derived drugs and biosimilar drug products will not be discussed fully in this book.

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2 Active Pharmaceutical Ingredients

Edward M. Cohen and Steven Sutherland

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INTRODUCTION

Active pharmaceutical ingredients (APIs) are also known in regulatory and pharmacopeial parlance as "drug substances." Additional terms frequently employed in commerce and the literature are bulk pharmaceutical compound, bulk actives, and "active ingredient." All terms relate to the same "article." New chemical entities (NCEs), also termed new molecular entities (NMEs), refer to drug substances that are first to enter the drug regulatory arena under the banner of a New Drug Application (NDA). The term "official substance" is defined in the United States Pharmacopeia (USP) as a drug substance, excipient (frequently termed inactive ingredient), dietary ingredient, other ingredient, or component of a finished device for which the monograph title includes no indication of the nature of the finished form [1]. Official substances are the subject of formal monographs in the USP or The National Formulary. Drug substance (API) monographs grace the USP exclusively. The other official articles noted are in other sections of the compendia. Not surprisingly, the end use of the API is to produce a drug product, which is the final

form of the drug substance administered to patients. Drug products are the subjects of companion monographs to the API in the USP. The ultimate safety and efficacy of the finally administered drug product are dependent on the assurance of the consistency of the physical and chemical properties of the API. This chapter will focus on the plethora of issues involved with the API, which must be considered when developing a generic drug product. In particular, the point of establishing specifications for critical quality attributes of the API will assure that the generic drug product, employing the API material, will have consistent in vitro/in vivo characteristics, batch after batch. As part of the routine evaluation of the compendial status of an API, in addition to the USP, the European Pharmacopeia, Japanese Pharmacopeia, British Pharmacopeia, Indian Pharmacopeia, the World Health Organization, and other "recognized" compendia should be checked to verify the presence or absence of published "official monographs" for the API.

A published overview of the regulatory oversight for both drug substances and drug products provides an excellent starting point for the particular issues that a firm faces when attempting to file an Abbreviated New Drug Application (ANDA) for an API [2]. The reference provides detailed accounting of all relevant U.S. Food and Drug Administration (FDA) documents and guidances covering the areas of concern with the focus on U.S. regulatory issues concerning APIs. Because the FDA does update "Guidances," it is important to continually scan the FDA website for guidance updates and new guidances.

SOURCES OF APIs

The three most commonly recognized categories of APIs are synthetic, semisynthetic, and natural. The latter category, natural, refers to the source of the API as being derived directly or extracted from natural sources. The category of semisynthetic indicates that a starting "intermediate" for the preparation of the API was derived from natural sources. The "isolated" intermediate is then converted synthetically to the final API. Synthetic APIs are obtained directly by chemical conversion of intermediates. It is not uncommon to see the market introduction of an API pioneer compound as a natural product, which is subsequently produced by a semisynthetic procedure. An example of the transitioning of an important API from "natural sourcing" initially to semisynthetic sourcing is paclitaxel [3,4]. In the arena of synthetic APIs, the transitioning that frequently occurs is that the initial drug product launch by the pioneer drug firm employed the API produced by a defined synthetic process. Subsequently, the pioneer product producer changes the API synthetic process. There is no requirement that the specific synthetic pathway be identified for the API as the product matures in the marketplace. It is not uncommon to see alternate "morphic" forms of the API enter the marketplace. When such changes occur for the pioneer product (originally approved NDA product), there may be labeling issues that need to be addressed for the "generic" equivalent product(s).

The USP has classified a category of drug substances as "complex active ingredients" [5]. This grouping of compounds includes biological and biotechnological drug substances and complex natural source drug substances. The traditional APIs are referred to as "noncomplex actives." This chapter will only focus on noncomplex actives.

PATENT RESTRICTIONS AND EXCLUSIVITY GRANTED TO AN NDA SPONSOR

The filing of an NDA with the FDA for a drug product made with an NCE results in the listing of "relevant" patents and periods of "exclusivity" for the approved drug product (frequently identified as the "listed drug"). This listing occurs in the FDA "Approved Drug Products with Therapeutic Equivalence Evaluations" and is referred to as the "Orange Book." The FDA now provides all of this information online at their website (http://www.fda.gov/cder). For an API supplier, the listed patents in the electronic Orange Book normally provide only those patents that protect the NCE (compound and method of use) as well as formulation patents (presumably those relevant to the filed drug product). Current issues concerning the listing of patents in the Orange Book are covered in Chapters 1 and 14 of this book. What is not a required listing in the Orange Book are process patents for the manufacture of the API or critical intermediates for the API, beyond the original patent(s) governing the NCE itself. This point is covered by a section of the Food Drug and Cosmetic Act, which authorizes an API supplier or an authorized party/agent for the API supplier to write to an NDA sponsor and request a listing of all relevant process patents that cover the filed NCE [6]. This is a fee for service request, with a maximum allowed charge of $500 for the service. The relevant U.S. Code information concerning patent infringements and penalties for infringement cited in Ref. [7] can be found at the website for the US Code.

With this list of process patents, the API supplier must now review all patents cited as well as conduct independent patent searches for all patents relevant to the NCE, which issued or were applied for in and outside the United States. This search should include not just the NDA sponsor but also any issued patent concerning the drug substance or any pivotal intermediate involved in the synthesis of the final drug substance. Specific aspects of the NCE that may be covered by process patents and other nonlisted patents in the Orange Book include particle size/surface area, morphic forms (polymorphs, hydrates, and solvates), and impurity/purity characteristics. The objective of the patent search is to determine what synthetic route to exploit for the manufacture of the target API, which will be noninfringing and cost effective and will yield finished API of appropriate quality and physical attributes suitable for formulation of the material into the targeted drug product for filing an ANDA.

Finally, with respect to "exclusivity" for the filing of an NDA, incorporating an NCE, the current regulations allow for a 5-year period of exclusivity before an ANDA can be filed incorporating the same API as the NCE. A different period of exclusivity is provided for the filing of formal supplements to NDAs, which is based on providing clinical data as part of the supplement. These points are covered in detail in Chapters 1 and 14 of this volume.

COMPARISON WITH INNOVATOR API

The challenge that the API supplier/manufacturer faces in entering the market place is to assure the user of the material that the API will be comparable with the innovator or pioneer drug substance, which is employed in an approved NDA drug product.

Current FDA requirements regarding the filing of an ANDA for a single-component listed drug product include that the API must be the same chemical entity, which is contained, in the approved NDA listed drug product. The critical aspects of sameness or comparability for the "generic" API versus the innovator API include three realms: chemical structure, impurity profile, and physical form.

Chemical Structure

Same chemical entity, including

- Salt or free base/acid form
- Isomeric composition
- Hydrate, solvate, or polymorphic form (see "Physical Form" for more details about the allowed latitude for variances)

Impurity Profile

- Establish the total impurity profile for replicate batches of the final process material (specified as well as unspecified impurities)
- Determine if there are impurities in the generic API, which are not present in the innovator API, and the relative level of such impurities
- List the total impurity profile for the generic API

The FDA Guidance "ANDAs: Impurities in Drug Substances," issued June 2009, is the current benchmark for categorizing, quantifying, specifying, qualifying, and reporting on impurities in generic APIs [6]. Part of the impurity assessment is reporting, identification, and qualification threshold. There is a very detailed "Impurities Decision Tree" in the guidance, which needs to be reviewed in depth when an issue arises about unknown impurities, or impurities whose safety profile cannot be gleaned from the literature and, more importantly, that impurity does not appear to be present in the innovator drug substance. Based on the guidance above, the critical aspect of dealing with "impurities," which includes organic impurities (process and drug related), inorganic impurities, and residual solvents, appears to focus on the issue of relating the levels found in the API to established pharmacopoeial standards or known safety data. A critical cutoff point for the organic impurities appears to be a level of 0.1%. The API manufacturer is encouraged to try to reduce the level of detected, individual impurities to levels of less than 0.10%. As far as impurity specifications are concerned, the issue is to have in place validated assay procedures than can assure a level of detection and a level of quantitation for all impurities. Maintaining individual impurities below 0.10% and assuring that the total of all specified and unspecified, identified and unidentified impurities at a level of 1% is likely to satisfy FDA concerns about the impurity profile for an API. On an individual basis, levels can be specified for individual impurities based on the process chemistry and stability history for the drug substance. The specification level has to meet benchmark standards of safety for use in the finished dosage form. The "ANDAs: Impurities in Drug Substances" guidance noted above goes into

great detail about qualifying impurities and developing specifications for the impurities in APIs. Finally, the FDA advises in the Guidance (see Section L3b) that one should compare the impurity profile of the generic drug substance with the process impurity profiles found in the innovator's marketed drug product (looking at three or more different lots of the innovator's product). A final comment about this point is that today's innovator product may be made with the drug substance synthesized by a different process than the originally launched innovator product. The generic API may be synthesized with an expired patented process of the innovator resulting in an impurity profile, which may be different from that found in today's innovator drug product. There is no benchmark "fingerprint" of the original innovator drug substance to make any comparisons of the original impurity profile with the current impurity profile of the innovator. An interesting issue is that if there was a USP monograph for the "innovator drug in place, prior to the point in time of submitting an ANDA for the drug product, a public standard would be available to establish 'objective' boundaries for critical quality attributes for the drug substance" [?]. Subsequent changes in the pioneer impurity profile might require update of the USP monograph. However, the initial impurity profile testing requirements were presumably part of the original USP monograph testing requirements and as such would still be available for comparative testing. Today's newer analytical technologies such as near infrared will permit more incisive analysis of the innovator drug product so that, even in the absence of a USP monograph, the ability to carry out a fingerprint of the innovator product (search for the impurity profile of the drug substance therein) is within technical boundaries for getting reliable information.

Physical Form

Another critical aspect of the API comparability to the innovator API is the physical form. This generally falls in the domain of the "morphic form," including particle size distribution. The term "morphic form" includes variances in crystal form (amorphous versus crystalline), polymorphism, solvates, and hydrates. Current precedents indicate that variants of the morphic form of the pioneer NCE can be incorporated into ANDAs, if the ultimate test for demonstration of the bioequivalence of the ANDA drug product to the pioneer listed drug product is successful.

Related aspects of the physical form of the API, such as particle size distribution, are important with respect to the in vitro dissolution performance of the finished dosage form. As noted above, the final dosage form developed by the ANDA sponsor must meet the FDA Office of Generic Drugs benchmark of "bioequivalence," which frequently is related to the in vitro dissolution performance of the dosage form. Thus, the physical form characteristics of the API need to be controlled such that, once bioequivalence is demonstrated versus the innovator product, subsequent batches of the API will provide the same performance characteristics to the final dosage form.

Developing final specifications for the API is based on establishing the desired chemical and physical profile of the API. The API suppliers frequently develop particle size "grades" for individual customers of the same API. It is very important to have similar, preferably identical, test methods at the API source and the API user

laboratory to avoid any confusing test results over time. An interesting practice that can serve the purpose of confirming the consistency of the physical form of the API is to employ optical microscopy as a routine inspectional test for individual batches of the API. The key in such a test is to assure that representative samples of the API batch must be examined in using the test to confirm the comparability of the product, batch after batch.

SPECIFICATIONS

The specifications developed for a new generic API must meet all USP monograph requirements, if a USP monograph exists for the API, as well as to satisfy all the current FDA/International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidances concerning impurities, residual solvents, and other specified attributes. The scope of specifications for an API will typically include

- Identity testing
  - Active moiety (IR preferred as well as specific chromatographic procedures)
  - Identification of specific counter-ions if API is a salt
- Impurity testing (includes degradants formed post-manufacture of the material)
  - Specified identified and specified but unidentified, individual, and total
  - Residual solvents (including USP organic volatile impurities)
  - Heavy metals (elemental impurities and/or other specific elements)
- Other specified tests
  - Morphic form, including particle size
  - Others (such as water, pH, and assay)

The USP has recently posted on its website a guideline for describing the content of a typical USP monograph. The terminology in the guideline is consistent with all current ICH practices and descriptors [8].

All test procedures should be validated in accordance with standard practices. It is important to note that, in the absence of any waiver, all specifications must be met through the designated shelf life or expiry dating or re-test date for the material. Part of the development of final specifications is the performance of stability studies for the material in the final container closure system in which the material is sold to the API consumer. An important part of the API process is to establish user-friendly "Certificates of Analysis." To the extent possible, all test results should be reported with actual findings and not left to the end point of "Complies." The test method employed should be easily identified if compendial methods are used, that is, specify the exact test method used. A critical factor in developing specifications is to have available well-defined reference standards for all tests that require a standard. In the absence of a USP monograph (or any other major compendia, such as the European Pharmacopeia, British Pharmacopeia, Japanese Pharmacopeia, and the World Health Organization), which typically defines which tests need a reference standard, the API supplier needs to follow established practices to develop and

provide to the drug product developer/manufacturer appropriate reference standards for the conduct of those tests requiring such standards.

DRUG MASTER FILE

A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storage of one or more human drugs. See the FDA website (http://www.fda.gov/cder/guidance/dmf.htm) for full details. Upon submission of a complete DMF, the FDA assigns a number to the DMF. The number entry becomes part of the DMF database.

One can search the DMF database and obtain information such as the name of the article included in the DMF, the name and address of the sponsor or holder of the DMF, and the date of original submission. The filed DMF is typically used in the generic drug environment to support the filing of an ANDA. A DMF holder provides letters of authorization to the FDA and the ANDA sponsor indicating that the FDA can refer to information in the DMF to support the filed ANDA, which utilizes the API for the drug product, which is the subject of the filed ANDA. There are five types of DMFs. The Type II DMF is limited to the drug substance or drug substance intermediate and the materials used in their preparation. A drug product can also be the subject of a Type II DMF. The FDA does not approve DMFs but can question the content and hold up a filed ANDA, which employs the particular API that is the subject of the DMF, until satisfactory responses are received. The DMF sponsor is required to update the filed DMF annually with information concerning any changes that were made in the manufacturing or controls employed for the production of the API, including specifications and test methods. As part of the procedure and practice of making any changes to a filed DMF for an API, the DMF holder is requested to notify all "customers" who purchase that API, and who have referenced the particular DMF in their ANDA, of such changes. The ANDA holder then is obligated to incorporate the information into its filed ANDA. Such incorporation may range from including the information in the Annual Report for the ANDA, file a Supplementary Changes Being Effected Supplement (CBE) to the filed ANDA, or file a Prior Approval Supplement (PAS) with the FDA for the filed ANDA.

An important aspect of developing APIs is to have a complete understanding of the chemical class of the drug substance being produced and identifying at an early stage what special handling issues may be needed for the particular API at issue. These include APIs in the category of controlled substances (follow mandates and dictates of the Drug Enforcement Agency for control and containment). Additional categories requiring special considerations are certain types of hormonal products and cytotoxic compounds. These handling precautions normally would get entered into batch manufacturing records, Material Safety Data Sheets, and on Analytical Test Methods. The required handling precautions should follow the trail of movement of the API all the way to the final user. There are a number of websites, including the USP, where MSDSs can be reviewed for the terminology and handling precautions cited for compounds in all risk categories. An interesting approach is to

"browse" the USP where a large number of monographs, both for APIs and for dosage forms, contain cautionary statements. The need for cautionary statements really falls into three sectors at the dosage form development site:

1. Laboratory and quality assurance personnel who handle the compound for "testing"
2. Drug product development personnel
3. Finished dosage from manufacturing/packaging, quality control, and stability testing personnel

Finally, there are consulting services that can provide counsel on environmental handling issues for the API and the drug product incorporating the API related to Occupational Safety and Health Administration, Environmental Protection Agency, and cleaning validation.

REGULATORY OVERSIGHT OF API MANUFACTURERS

For a new manufacturer or a new API manufactured at an established site previously registered in filed DMFs, the FDA normally requires that a successful preapproval inspection occurs before the agency would grant approval to the filed ANDA, which incorporated the particular API. Typically, such inspections tend to be vigorous and cover both current good manufacturing practices as well as scientific, technological, and related matters such as environmental, Occupational Safety and Health Administration, compliance with Department of Transportation, and the like. A very detailed FDA guidance has been issued regarding "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Q7A, August 2001)." This guidance covers every aspect of the API manufacturing operation, from start to finish, including documentation at all stages as well as distribution and recalls.

BULK ACTIVE CHEMICAL, POST-APPROVAL CHANGES (BACPAC)

- BACPAC I: Intermediates in Drug Substance Synthesis Formal Guidance. Current update is February 2001.
- BACPAC II: Final Intermediate to Drug Substance. PQRI final draft, representing consensual industry input, will be provided to the FDA for crafting a "Draft Guidance."

The BACPAC guidances govern postapproval changes to the manufacture of active pharmaceutical ingredients [6]. BACPAC I covers the control of intermediates in drug substance synthesis and is a formal guidance. The current update is February 2001. BACPAC II covers changes in the final intermediate to finished drug substance. This is still not a formal guidance but is a final draft, representing consensual industry input. The information pools in the guidance cover all aspects of the API process ranging from manufacturing, ingredient sourcing, site changes, specifications, and test methods. In reviewing the guidance content, the two focal points that emerge are what impact does the change or changes have on the impurity profile and physical

properties of the material as it relates to the end use of the API final intermediate or the final API. As far as the API manufacturer is concerned, any change will become incorporated into the Annual DMF report. With respect to the user of the API, the issue is how to report certain types of changes (Annual Report, Supplement Changes Being Effected, or a Prior Approval Supplement). As previously noted, the DMF holder has a legal obligation to notify an ANDA sponsor of changes that have been implemented in the manufacture, processing, or controls of the API. The critical point in the BACPAC guidance is that the API manufacturer is expected to obtain comparison data of the material that underwent the change with the prior process material. Typically, a comparison of the prematerial and postmaterial at the level of multiple batches is requested [9]. Both the API-DMF holder and the ANDA holders need to have clear consensual views of what changes have been made and how to deal with the changes in a very consistent manner. The BACPAC concept came at the heels of the scale-up, postapproval changes concept for the finished dosage form. The simple fact is that some changes can be made and, based on the comparison data, may fall into the category of Annual Report in today's climate. This is a savings of time, energy, and resources for all parties concerned: DMF holder, approved ANDA holder, and the FDA. What is a surprise is that at the beginning of June 2006, the FDA announced that the BACPAC I guidance was being withdrawn. The FDA rationale for this action was that the issued BACPAC guidances "were not consistent with the cGMP for the 21st Century." One can infer that efforts are underway to replace the withdrawn guidances to better harmonize the regulatory efforts for both APIs and finished drug products [9].

TECHNICAL PARTNERSHIP BETWEEN THE API MANUFACTURER AND THE DRUG PRODUCT MANUFACTURER

A strong interactive working relationship between the API source and the API consumer is important to assure that there is harmony and consensus in the filing of ANDA specifications for the drug substance with the filed DMF of the API supplier. This relates, in particular, to specifications and test methods. The auditing of the API source by the API consumer should be based on mutual respect and understanding of differences. Such a relationship will lead to timely resolution of technical issues. Further with the implementation of BACPAC I and BACPAC II, it is even more critical that each side understands the issues and practices of the other side. An initial site audit of an API supplier is common practice when working with a new source of an API. This audit should be followed up on some periodic basis, particularly if some issues were discovered during the initial audit. As the FDA inspectional history for an API supplier evolves, some determination can be made about the need and frequency for follow-up audits.

IDENTIFYING AND QUALIFYING API SOURCES

The DMF track record and FDA inspectional history are typically a starting point for establishing the qualifications for an API source. As previously noted, one can go online to the FDA website for a listing of all DMFs for a particular API. The FDA inspectional history can be obtained under Freedom of Information from various

search engine services for any given API manufacturer. One needs to know the particular site of manufacture for the API supplier for the particular API of interest, if the API manufacturer has multiple sites. The FDA inspectional history includes FDA "483s" and "EIRs." The FDA "483" is the inspection report listing "observations" issued to a firm immediately following a site inspection. The FDA Establishment Inspection Report or "EIR" is the FDA's internal report about the inspection findings. For both types of documents, the FDA dockets management branch issues "purged" documents, which exclude certain "confidential information."

A number of search engine services can provide detailed information about current manufacturers/marketers of specific APIs. The input requirements to get the search started are the CAS number and any recognized/official names for the API. By pooling the information from the DMF database, FDA inspectional history, and listings of identified suppliers (which often includes some marketing statistics for the firm and API), one can very quickly identify the pool of suppliers for just about any API. Following the identification of a primary source for an API, it is often common practice to establish alternate sources in the case of an unexpected event, which might block the primary source from serving the needs of the ANDA drug product developer.

A critical factor in moving ahead with an alternate source of the raw material (frequently referred to as "ASRM") is to have established and well-defined specifications for all critical quality-control attributes to minimize any adverse effect on the ANDA drug product formulation and manufacturing process. These specifications are provided to the potential ASRM and based on the response information provided as well as the evaluation of samples of the API can provide the basis for determining whether the ASRM material will fit the "boundaries for the filed ANDA." Here, the issue of comparability, previously discussed in the context of the primary source of the API versus the "innovator," now becomes the comparability of the primary API source versus the ASRM [10]. The timing to complete the qualification of an ASRM typically can vary from 6 to 12 months, if the testing includes manufacture and accelerated stability studies of test batches of the drug product. The completion of qualification would then be followed by filing an amendment to the filed ANDA.

A frequent issue for identifying an API source for an NCE is that, at the early stages of the NCE history, there may not be any listed source for the API. Further, there may not be any solicitation for the compound. Here, the best approach is to understand the chemistry of the NCE and identify API sources that have been involved with that chemistry before. Alternatively, look for API sources that typically stay on the forefront of NCEs. A strategy that may be worth pursuing is to start the API sourcing process immediately after an NCE enters the marketplace and when it is clear that the NCE will achieve an attractive market share.

CONCLUSION

The successful development of a generic drug product starts with the API. It is critical to understand the basic science underlying the targeted listed drug API as well as the intellectual property that "limits" the horizons for the synthesis and specifications for the generic API. Further, companion challenges that confront both the API

supplier and the generic drug product developer are the evolving milieu of regulatory and compendial forces that provide acceptance boundaries for the purity, safety, and efficacy for the API. Additionally, the regulatory milieu covering current good manufacturing practices, including manual and electronic documentation, must be respected and enforced at both the site of production of the API and the site of manufacture of the final dosage form targeted for marketing. On a going forward basis, the API supplier will be held accountable for the consistency of the chemical and physical properties of the material being produced on a routine basis. Good science and mutual respect for the technical issues must prevail in the relationship between the API manufacturer and generic drug product developer to assure the continued production of generic drug product, which stays within the performance boundaries of the originally filed exhibit batch(es) in the filed ANDA.

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3 Analytical Methods Development and Methods Validation for Oral Solid Dosage Forms

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INTRODUCTION

Development of oral pharmaceutical drug products presents many technical and regulatory challenges. Specifically, these include proper characterization of active pharmaceutical ingredients (API), assurance of compatibility of inactive ingredients with the active components over the shelf life of the product, processing, manufacturing, quality controls, and compliance with code of federal regulations and draft federal regulations under the Code of Federal Regulations (CFR) provisions for comments and approval process at the U.S. Food and Drug Administration (FDA).

Code of federal regulations mandate that any generic drug product intended for human use must be approved by the Agency for marketing a generic drug product and its multistrengths in the United States. These code of federal regulations provide assurances to the consumer that these generic drug products are safe, therapeutically equivalent, and effective in the same manner as the innovator or branded drug products approved previously as New Drug Applications (NDAs) by the FDA. Additionally, the quality-control information presented by a generic product manufacturer or sponsor in the Abbreviated New Drug Applications (ANDAs) documents the evidence that the API used in the dosage form—may it be a parenteral, oral solid dosage, topical, inhalation, implant, or a specialized delivery system form—is rigorously tested to comply with the regulatory mandates of acceptable limits of compendial or regulatory specifications mutually agreed upon by the sponsor and the Office of Generic Drugs (OGD) division of the FDA. The reader is referred to numerous Code of Federal Regulations and Guidance issues on this topic [1–8]. For the new millennium, the FDA has implemented the 21st-century pharmaceutical current good manufacturing practices (cGMP) initiative and quality-based design for new drug product approval of the innovator (brand) company. The OGD in the FDA has developed a questions-based review system for the generic company to implement a questions-based development (QbD) program in development and manufacturing of generic products and to assess generic product sponsors' QbD in their ANDA filings.

Method Development and Its Importance

Method development in the generic product design phase (which is intended to define the target product quality attributes profile) begins with full analytical testing and reproducible characterization of the API for which there is a Drug Master File (DMF) registered with the Agency. It is becoming imperative to apply QbD principles for method development. The DMF submitted to the FDA by the API manufacturer contains confidential details of the synthetic process, drug substance form, and purity, along with identity of impurities listed in the API specifications and their pathways of formation. An active partnership between the API vendor and ANDA sponsor who is developing the finished dosage form is essential to assure that the API meets the cGMP requirements for testing and stability with adequate control on the manufacturing process. In case any deficiency is observed by OGD, the API vendor has to address their response to the deficiency related to the API before the ANDA sponsor can address their response for the deficiency related to the chemistry, manufacturing, and control (Chemistry, Manufacturing, and Controls section of ANDA) of the finished dosage form.

Analytical method development and its validation play a very vital role in the process of API selection for generic dosage form development. Typically, the analytical chemist utilizes numerous literature sources such as Summary Basis of Approval for the innovator drug product NDA and technical literature in numerous medicinal chemistry and analytical chemistry journals, as well as Internet Web sites dedicated to publication of original articles on pharmaceutical entities and pharmaceutical drug product development. Frequently, the API supplier provides to the ANDA sponsor certain critical documents such as Material Safety Data Sheet, Certificate of Analysis listing the tests, API specifications, and results of a particular lot and current analytical methods used by the API manufacturer, such as high-performance liquid chromatography (HPLC) methods for identification and quantitation of the active drug and known and unknown impurities. This helps the method development chemist to get a head start in completion of preliminary method development work and to establish preliminary API specifications for release of the API and support the formulation pharmacist in developing the dosage form for an ANDA filing. If the API is listed in a compendial monograph (United States Pharmacopeia [USP], European Pharmacopeia, British Pharmacopeia, Japanese Pharmacopeia, etc.), the chemist can use the monograph listed test method as a starting point for method development.

Once the API method is developed, the analytical chemist can begin the method development for the dosage form. Typically, placebos of dosage forms of tablets or capsules are utilized to assure that the inactive ingredients used by the formulation scientist do not interfere with the identification and quantitation of the target analytes (active or know impurities) in the dosage form. Establishment of method specificity, sensitivity, linearity, reproducibility, precision, and accuracy for quantitation of the drug in a dosage form is pursued to assure that the method can be used for evaluation of dosage form stability. More specifically, comparative in vitro dissolution performance of the oral dosage formulation by compendial or other suitable dissolution test methods in relevant physiologic pH medium recommended by the FDA in bioguidances is evaluated along with a lot of the brand (innovator's) drug product of identical strength. Frequently, specific methods for detection and quantification of trace amounts of impurities are developed to assure that the product complies with compendial (USP, British Pharmacopeia, European Pharmacopeia, Japanese Pharmacopeia, etc.) or noncompendial specifications for organic and inorganic impurities to assure proper identity, purity, and safety of the drug product during the product shelf life, typically a minimum of 2 years from the date of its manufacture.

In addition, analytical methods are required for the purpose of fully understanding the innovator (brand) product formulation and its component and quantity used in the formulation. This quality target product profile forms the basis of design for generic product development. This type of work aiming at defining target product profile is usually referred to as deformulation or reverse engineering. Although these types of methods are not required for ANDA submission, it plays a key role in generic drug product development for the formulation design and development. Information such as the excipient grade and amount (examples are the polymer content and its molecular weight distribution), hydration level of a salt, or neutral excipient in the brand product formulation can be critical for the generic formulation scientist to

develop generic product formulation to assure that the generic drug product is bioequivalent and stable, in addition to its quality and manufacturability in batch sizes exceeding 100,000 units.

Analytical method is an integral part in a QbD system. It is used to collect in-process information for timely control decisions. It is used for monitoring and trending process parameters and for monitoring product quality. The QbD system provides data to better understand the process. The data collected using analytical test methods can be used for continued process and product improvement. Analytical method for a specific drug product line and its extensions is part of the control strategy to assure process performance and product quality. Analytical methods and product specifications developed based on numerous product batch performance also provide information for risk management, which includes assessment of product efficacy and safety.

While scale-up of the new generic oral dosage form in one or more strengths is ongoing to prepare clinical supplies for pilot bioequivalence studies, in-process testing and methods for such testing are developed to assure proper control of the process and the quality of the drug product. Generally, test methods for finished dosage forms are stability indicating, and the information generated from accelerated stability test results of the drug product in the final packaging intended for commercialization is used by the product development team of scientists and regulatory staff to determine the drug product specifications, including those not specified by the compendia. The prime objective of the analytical chemist is to assure that the generic drug product in a final commercial packaging is in compliance with compendial standards in identity, potency, content uniformity, dissolution, and acceptable limits on impurities and related substances.

In this chapter, we have placed a strong emphasis on the importance of robust method development, in-process control methods, and validation approaches taken to finalize such methodologies for development. Also emphasized is the importance of documentation of dissolution and finished drug product specifications for the drug product for submission in the Chemistry, Manufacturing, and Controls sections of the ANDA, which is mainly reflected in Modules 2 and 3 of the common technical documents format required recently by the FDA. The reader is referred to several literature sources and Center for Drug Evaluation and Research guidances available on this topic [2–8].

METHOD DEVELOPMENT

Analytical test methods are used to generate data for establishing the identity, potency, purity, and overall quality of the drug substance and drug product. A well-developed test method not only can control the quality of the product but also can speed up the development process by shortening the development time for raw material vendor selection, qualification, and formulation screening. Further, a well-developed test method can enhance the efficiency for the downstream product launch and routine release tests. Analytical test methods are the stakeholders of product development in providing accurate and reliable data to support product formulation specifications, packaging specifications, process development, characterization and

process controls, stability and release, pharmacokinetics and bioequivalence, and regulatory filing.

The time and effort spent in developing a robust and efficient test method is well worth it for the downstream method users such as laboratory technicians and chemists in the quality-control laboratories of the generic drug manufacturer. A test method with shorter run time and less use of solvents can save much labor and cost for the quality-control laboratories for years to come in future production.

The performance of a test method is determined primarily by the quality of the procedure itself. Timing is critical for method development because "first to approve" means substantially high profit versus the late comers.

Before developing a test method, one must define the scope and requirements for the test method. The objectives for the test method will ultimately define the extent of the development and optimization. The requirements for the test method include the following issues to be addressed: (1) regulatory compliance, (2) technical requirements, (3) practical requirements, (4) validation requirements, and (5) transfer requirements. Once these requirements have been addressed, the method development scientist can start with a literature search and information gathering. A plan can be developed with clear objectives for the method, such as requirements for the separation of known compounds, chromatographic procedures, and a targeted timeline. Adequate resources should be allocated for method development before initiating the bench work. Typical sample solution and standard solution can be used to evaluate different chromatographic conditions. It is suggested that one should fully utilize the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines [9–11] regarding the reporting threshold, identification threshold, and qualification threshold. The ICH and USP chapter <467> defined residual solvent classes, and allowable limits can be used for method development and release specification. When the main objectives are met, the test method can be further optimized to make it more economical and user-friendly. Once the optimization is completed, the method is challenged to see if it can be validated. For chromatographic procedures, the challenges are often method sensitivity and method selectivity. These method prevalidation evaluations can determine if the method is ready for validation.

The following are the commonly needed test methods in the development and manufacturing of generic oral pharmaceutical solid dosage forms.

API Test Methods

The objectives for the development of the API test methods are for raw material vendor selection and raw material release. Where multiple vendors of an API are available, test methods are needed to characterize each lot of API and evaluate the raw material quality. The quality and characteristics of the APIs can often influence the formulation development concerning the dissolution profile and stability of the final dosage form in development.

Typical test methods for the API release include identification, assay, chromatographic purity, residual solvents, particle size measurement, and polymorph determination in addition to commonly required compendial tests such as water content (loss

on drying or Karl Fisher test), residue on ignition, melting point and range, specific rotation, crystallinity, heavy metals, pH, and sulfide.

Very often, the assay and chromatographic purity tests are conducted using HPLC procedures. Most of these HPLC procedures are based on reverse-phase chromatography. The knowledge, skill, and experience of the method development scientist in chromatography are critical for developing an accurate, precise, specific, rugged, and robust test method with good linearity and range. The development of a chromatographic purity test method is often more challenging than the assay because it is necessary to have the desired selectivity and sensitivity for separating all impurities at approximately 0.05% level. In particular, separating structurally similar isomers of the actives such as double bond shifts on a carbon ring structure or optical isomers (chiral molecules) poses challenges for even the experienced method developer. Figure 3.1 is a typical chromatogram for the chromatographic purity test of a pharmaceutical raw material.

Sometimes, semiquantitative thin-layer chromatography (TLC) test methods are needed for testing of impurities in the API. The development of such test methods requires the selection of the appropriate TLC plate and optimization of the developing solvents. Due to the semiquantitative nature of the TLC test method, an HPLC method is often used to quantitate the impurities.

The residual solvent test methods are often based on gas chromatography (GC) [12]. Either headspace or direct injection mode can be used for the residual solvent test method. Because GC is a very mature field of the pharmaceutical sciences, separating residual solvents can often be resolved with limited development time due to the high selectivity of the modern capillary GC columns. Often, it is desirable to find a laboratory-friendly and GC-compatible solvent that can dissolve both the API and the target analytes of the residual solvents. Figure 3.2 is a typical headspace residual solvent test method, where commonly used organic solvents are fully separated by GC.

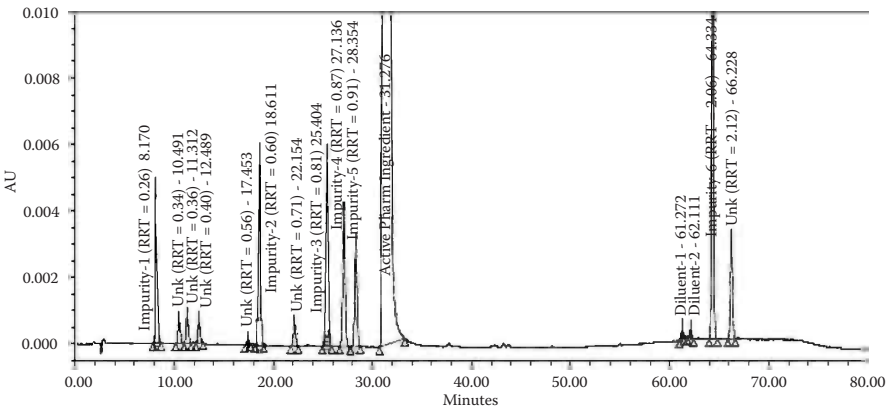

FIGURE 3.1 Typical chromatogram for the chromatographic purity test of a pharmaceutical raw material with spiked standards of known impurities.

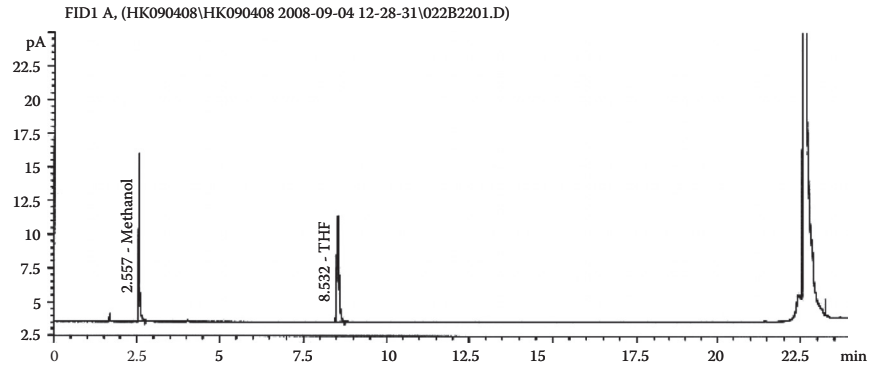

FIGURE 3.2 Typical headspace residual solvent test method chromatogram.

API test methods are also involved in alternate API supplier qualification. The API supplier approved in the original ANDA can be changed due to business or quality reasons. When there is such a need of switching API supplier, the alternative API raw material needs to be qualified. The new API raw material has to be characterized to compare with the original API raw material for its physical and chemical properties. New lots of finished dosage form product using the alternative API need to be manufactured and placed in stability to demonstrate the quality. All data collected and assured for quality need to be filed for approval of the alternative API supplier.

In-Process Test Methods

The objective of an in-process test method for oral solid dosage forms is to obtain information to control the pharmaceutical manufacturing process. Typical in-process test methods include loss on drying or use of Karl Fischer for water content determination (to control the moisture content in the drying process), residual solvent (to control the residual solvent in the blend granules), and blend uniformity testing. The loss on drying (or Karl Fisher) test method is straightforward and usually does not require method development. The residual solvent test method and blend uniformity test method would require method development. Often, the blend uniformity (for granules), content uniformity (for finished dosage form), and assay (finished dosage form) share the same chromatographic conditions with separate sample preparation procedures. Therefore, method development is often conducted concurrently for these three tests (assay, content uniformity, and blend uniformity).

Finished Dosage Form Test Methods

The objectives for the development of the finished oral solid dosage form test methods include formulation identity, in vitro dissolution screening for acceptable performance within tolerance limits, and dosage form release. Very often, the dissolution test method is needed first for the in vitro characterization of the innovator's

reference product versus the in-house formulation. The screening dissolution test method is not necessarily the same as the dissolution test method for product release in quality control. The in vitro dissolution test method used for formulation development needs to be discriminative for different formulations and yet be biorelevant to predict performance of the dosage form in vivo. USP Apparatuses 3 and 4 are used for development purpose. The product release dissolution method can be referenced to compendial requirements [13] for USP/National Formulary (NF) listed dosage forms. In particular, the selection of the dissolution medium and test conditions, such as the type of apparatus and the rotational speed of either the paddle or the basket, are critical for the success of the test method. However, if the USP dissolution condition cannot be met yet the product is proven to be bioequivalent to the innovator's product, alternative dissolution method and condition can be submitted to USP for monograph update.

For a stable oral solid dosage form development, matching the in vitro dissolution profile with the innovator's or reference product is often the main concern for the formulator. Formulation support activity is then focused on the dissolution tests specific to the type of oral dosage form (e.g., immediate release, delayed release, extended release, or pulse release). When dosage form stability is also a concern for drug product development, assay and chromatographic purity test methods are often needed in addition to the dissolution test method. When possible, the use of the same chromatographic conditions for the assay and chromatographic purity tests can often save method development and method validation time.

Typical test methods for finished dosage forms include identification, assay, content uniformity, chromatographic purity, dissolution/disintegration, and hardness/friability. Additional test methods needed to support the product development are cleaning test methods for the equipment release, confirmation methods for the absence of actives in the placebo tablets, etc.

Method development has the following deliverables:

1. Specificity (i.e., the method has to be able to separate the target analyte from other components and the method can quantitate this analyte without ambiguity).
2. Linearity (i.e., the method should operate in the linear response range of the detector). Although linearity is usually obtainable, occasionally the linearity cannot be met due to the nature of the detector used. In such cases, a multiple-point calibration curve should be established and used for quantitation.
3. The method is optimized (i.e., the analyte can be fully extracted from the sample matrix, and the separation conditions are at the optimal conditions).
4. Sensitivity (i.e., the test method can quantitate the target analyte at the required reporting threshold).
5. System suitability (i.e., all target analytes can be resolved well-defined, well-eluted peaks in a chromatogram, then the requirements for the column performance is well established, the instrument characteristics such as sensitivity and precision are established, and system reproducibility is established).

HPLC is most commonly used for the assay and chromatographic purity determinations because HPLC test methods can provide required accuracy, precision, linearity, sensitivity, ruggedness, and robustness. Many references have been published for HPLC method development and validation [14–18]. The method development should consider the choice of columns for normal-phase, reverse-phase, or ion chromatography. The mobile-phase selection and operational conditions should be optimized through the method development such as flow rate, column temperature, pH buffer, and ion-pairing agent. The detector used should have adequate sensitivity and dynamic response range. When the target analyte does not respond to the ultraviolet (UV) detector well, alternative detectors can be used such as fluorescent detector, electrochemical detector, evaporative light scattering detector, corona discharge detector, refractive index detector, nano-quantity analyte detector, or mass spectrometry. Where possible, an isocratic elution mode is preferred to a gradient elution mode due to the simplicity of operation and robust nature of the isocratic separation mode versus the gradient separation mode.

The sample preparation, seemingly simple but very critical, is usually the first step of a test method. The solvent used for the extraction of target analytes should be studied to obtain the maximum performance. Without adequate extraction, it does not matter how good a chromatographic procedure is; the method would not be able to deliver reliable results. During method development, sample handling conditions should be optimized. Factors to be considered for sample handling, in addition to organic solvent strength for adequate target analytes extraction, should include the solubility of the API and impurities, including the excipients, to avoid precipitation during extended sample analysis and sample storage time. The time spent for sample sonication should be optimized to have the analyte(s) fully extracted from the matrix yet not to the point where degradation would occur due to the energy input from the ultrasound sonication.

For chromatographic purity methods, obtaining the required sensitivity and selectivity of the method is usually a challenge. The quantitation limit should guarantee that the test method can quantify components at the required reporting threshold concentration level. When the product strength is low, the method sensitivity will become more critical and challenging for method development. A hormonal oral solid dosage form, such as oral contraceptives, is one of the examples of a low-strength drug product. The strength of these products can be as low as a few micrograms per tablet and usually composed of two actives in formulation. The test method should also have adequate specificity, particularly for stability-indicating capability. Forced degradation studies under thermal, acid, base, oxidation, and photodegradation conditions should be conducted to verify that the test method can reliably quantify degradation products. Typical experimental conditions for the forced degradation studies are as follows: storing solutions in a UV chamber, adding equal volume of 1 M phosphoric acid or HCl aqueous, adding 0.5 M sodium hydroxide solution, adding 2% hydrogen peroxide, or water, and heating to approximately 80°C for approximately 24 hours to obtain adequate amount of degradation. The recommended level of degradation is approximately 10% to 30% unless the maximum degradation conditions are applied. The conditions should be adjusted depending on the stability of the actives. Efforts should be made to correlate the amount of active degradation versus the amount of

degradation products formed, although it may not be possible to account for 100% of degradation products by the observed loss in actives. This mass balance checking should be performed for method validation study. It should also be considered when the method is applied to product stability study so that the decrease in assay value for the active(s) is mass balanced with the amount of impurities observed. The method specificity becomes more challenging when the product contains multiple actives and the strength of these actives differs in orders of magnitude.

In developing a dissolution method, one should consider that the medium used for the test should meet the sink condition for the in vitro test. For water-insoluble compounds, the dissolution medium may contain surfactants or organic solvents, although the latter should be avoided if possible. The assay for the drug release method can be a chromatographic procedure such as HPLC, a spectrophotometric procedure such as UV, or other suitable procedures. Shorter run times for chromatographic procedures are necessary due to the large number of samples to be analyzed for dissolution profiling studies. As mentioned earlier, compendial dissolution method should be considered first. Because the dissolution is formulation dependent, the alternative dissolution method can be submitted in the ANDA application and subsequently to the USP for monograph update if the drug product is shown to be bioequivalent to that of the innovator.

METHOD VALIDATION

Method validation is the process of demonstrating that the analytical method is suitable for its intended use. The validation process establishes documented evidence that provides a high degree of assurance that the test method will consistently provide accurate test results that evaluate a product against its defined specification and quality attributes.

Objectives of Method Validation

Validation of analytical methodologies is considered as an important task, occurring after method development and before method utilization, and is required in support of product registration applications such as ANDA and NDA applications to the FDA.

Method Validation Requirements

Compendial Analytical Procedures

The validation of a test method normally depends on whether the test method is a compendial method or a noncompendial method. The validation of compendial methods is described in USP <1225>. Users of analytical methods described in the USP and the NF are not required to validate accuracy and reliability of these methods but to merely verify suitability under actual conditions of use. The methods provided in official monographs have been validated by the laboratory submitting the monograph and may have also been verified by other laboratories designated by the

USP. For chromatographic purity methods, method sensitivity and selectivity under the actual conditions of use should also be demonstrated.

For API test methods, the compendial methods can be readily adopted for use with limited suitability verification. For finished dosage form product test methods, the suitability of the test methods to the specific formulation needs to be demonstrated through a validation procedure. Validation of compendial test methods for the finished drug product may include, but not be limited to, specificity, linearity, accuracy, precision, and solution stability. However, it should be noted that the compendial methods are not necessarily stability indicating. When the compendial method is used for such purpose, forced degradation studies are needed to demonstrate method specificity.

One should keep in mind that USP monograph procedures are regulatory procedures.

A regulatory analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the USP/NF are those legally recognized under Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) as the regulatory analytical procedures for compendial items. For purposes of determining compliance with the Act, the regulatory analytical procedure is used.

Noncompendial Methods

For the validation of noncompendial test methods, one should follow USP, FDA, and ICH guidelines. Four categories of analytical methods are classified in the USP <1225>.

- Category I: Analytical methods for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products fall under this category.
- Category II: Analytical methods for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products are in this category. These methods include quantitative assays and limit tests.
- Category III: Analytical methods for determination of performance characteristics such as rapid drug dissolution or drug release profile.
- Category IV: Analytical test methods for identification purposes.

In addition, there are tests classified as specific tests such as particle size analysis, droplet distribution, spray pattern, dissolution (excludes measurement), and optical rotation and methodologies such as differential scanning calorimetry, x-ray diffraction, and Raman spectroscopy.

The elements recommended for validation for each category of the test methods are shown in Table 3.1.

Because the validation of a test method is a matter of establishing documented evidence that provides a high degree of assurance of the suitability of the test method for its intended use, the documentation process usually includes a validation protocol, test data, and a validation report.

TABLE 3.1
Recommended Validation Characteristics of the Various Types of Tests

Type of Tests/ Characteristics	Identification	Testing for Impurities		Assay Dissolution (Measurement Only), Content/Potency	Specific Tests
		Quantitative	Limit		
Accuracy	–	+	–	+	+[a]
Precision-repeatability	–	+	–	+	+[a]
Precision-intermediate precision[b]	–	+[c]	–	+[c]	+[a]
Specificity	+[d]	+	+	+[e]	+[a]
Detection limit	–	–[f]	+	–	–
Quantitation limit	–	+	–	–	–
Linearity	–	+	–	+	–
Range	–	+	–	+	–
Robustness	–	+	–[f]	+	+[a]

Note: See draft guidance for analytical procedures and methods validation of FDA (August 2000). – signifies that this characteristic is not normally evaluated, and + signifies that this characteristic is normally evaluated.

[a] May not be needed in some cases.

[b] Ruggedness is considered as intermediate precision.

[c] In cases where reproducibility has been performed, intermediate precision is not needed.

[d] Lack of specificity for an analytical procedure may be compensated for by the addition of a second analytical procedure.

[e] Lack of specificity for an assay for release may be compensated for by impurities testing.

[f] May be needed in some cases.

One should keep in mind that although a noncompendial procedure has been validated, when a compendial procedure exists, an equivalency study is needed for the regulatory submission to demonstrate that the noncompendial procedure is equivalent to the compendial procedure. The method equivalency study is discussed in Method Equivalency Study. When a legal dispute occurs, the compendial procedure will be used to judge the product quality and compliance with the regulations.

Development of a Validation Protocol

The development of a method validation protocol should be based on the requirements of the product specification and regulatory guidelines including internal standard operating procedures (SOPs). A protocol should include the target method to be validated, preapproved validation elements, and acceptance criteria. It should also describe the requirements for protocol execution, experimental design, a plan or procedure when acceptance criteria are not met, and reporting items.

Typical validation characteristics are as follows:

- Accuracy
- Precision (repeatability and intermediate precision)
- Specificity
- Detection limit
- Quantitation limit
- Linearity
- Range
- Robustness
- Solution stability
- Filter interference (where applicable)

System suitability evaluated during the method validation should be summarized in the method validation report and the finalized parameters for system suitability should be put in the test method. For example, the validation data indicate that the relative standard deviation (RSD) of six injections of the analyte in the working standard is close to but not more than 2.0%, the resolution between two closely eluting standards is close to but not more than 2.0, the tailing factor for the analyte in the working standard is not more than 1.2, and the theoretical plate number of the analyte in the working standard is approximately 10,000. Then, the above-mentioned parameters can be set as the system suitability requirements because the validation results have indicated that these parameters can provide assurance of the separation quality and repeatability of the test method.

Establishment of the acceptance criteria is based on the category of the test method. Typical validation elements and acceptance criteria for Category I methods of finished oral dosage forms are listed in Table 3.2. Typical validation elements and acceptance criteria for the Category II method (chromatographic purity) are listed in Table 3.3. Typical validation elements and acceptance criteria for the Category III test methods are listed in Table 3.4.

The Category IV validation element is specificity and the identification test procedure can be infrared spectrometry, TLC, wet chemistry, UV-visible spectrophotometry, etc.

The protocol can also define the procedure for handling situations where one or more validation elements fail to meet the acceptance criteria during the method validation. When such a situation occurs, the study director with the assistance of the chemist executing the protocol can assess the situation and determine with management approval:

- Whether the results can still be accepted with justification
- Whether a limitation to the method application can be set so that the failure of the method can be excluded outside of the method application range
- Whether the failing results need to be confirmed and an investigation may be needed
- Whether the method has a defect and needs to be modified and then revalidated

TABLE 3.2
Validation Elements and Acceptance Criteria: Category I

Validation Element	Acceptance Criteria
Precision	The RSD of six determinations (injections) of each analyte must be NMT 2.0%.
Accuracy	The average recovery for each analyte must be NLT 98.0% and NMT 102.0% for triplicate determinations at analyte concentrations of 80%, 100%, and 120% of the target concentration.
Specificity	1. No peak interference in the diluent and placebo injections at the retention time of the target analyte. 2. The target analyte peak is resolved from adjacent peaks. 3. The target analyte peak is pure by PDA analysis for forced degradation conditions.
Method linearity	These acceptance criteria must be met for a five-point concentration range of at least 80% to 120% of the target concentration. 1. The correlation coefficient (r) is NLT 0.995. 2. The percent bias of y-intercept is NLT –5.0% and NMT 5.0%.
Range	The precision, accuracy, and linearity criteria must be met from at least 80% to approximately 120% of the sample concentration. If the range is larger, report the largest range over which the acceptance criteria are met.
Ruggedness (intermediate precision)	1. The RSD of the spiked sample preparations from a second analyst, on a second instrument, and on a different day using a different column must be NMT 2.0%. 2. The RSD of the spiked sample preparations from both analyst one and analyst two must be NMT 5.0%.
Filter interference	The assay of a filtered sample must be NLT 98.0% and NMT 102.0% relative to the same sample prepared by centrifugation.
Solution stability (ambient or refrigerated temperature)	1. The assay of the sample preparation must not change by more than 2.0% in a specified time period. 2. The assay of the working standard must not change by more than 2.0% in a specified time period.
Robustness	System suitability criteria are met for the following method variations: 1. Variation of organic component in the mobile phase ±5% (relative) 2. Variation of ion-paring concentration of ±10%, when applicable 3. Variation of mobile phase pH of ±0.1 pH units, when applicable 4. Variation of flow rate approximately ±10% 5. Variation of wavelength ±2 nm 6. Variation of column temperature approximately ±5°C (where applicable)

TABLE 3.3
Validation Elements and Acceptance Criteria: Category II

Validation Elements	Acceptance Criteria
Precision	RSD is NMT 10.0%.
Accuracy	Recovery for target analyte is between 80% and 120% for spiked placebo samples for the method range.
Linearity	These acceptance criteria must be met for a five-point concentration range of at least LOQ to 150% of the target concentration: 1. The correlation coefficient (r) is NLT 0.99 for the method range. 2. The 95% confidence interval of the intercept includes the origin. If not, the intercept is NMT 100 ± 10% of the response of the standard concentration (at the specification level).
Range	The concentration at which the precision, accuracy, and linearity criteria are met. This range should be from the LOQ to 150% of the specification level.
Quantitation limit	The concentration at which the S/N ratio is approximately 10. The quantitation limit should be NMT the reporting threshold defined in ICH Q3B.
Detection limit	The concentration at which the S/N ratio is approximately 3. The detection limit should be NMT half of the reporting threshold defined in ICH Q3B.
Specificity	1. No peak interference in the placebo injection at the retention time of target analyte(s). 2. The known impurity peak(s) are resolved from each other and from the active substance peak(s). 3. The target analyte peak(s) are pure by PDA analysis under forced degradation conditions.
Ruggedness (intermediate precision)	1. The precision and accuracy acceptance criteria for a second analyst must be met for a standard spiked placebo solution on a separate instrument using a different column with sample solution prepared on a different day at the specification limit concentration level. 2. The combined RSD(s) of the analyte(s) for both analysts must be NMT 15.0%.
Filter interference (where applicable)	The peak area of each known impurity peak must be within 100 ± 10% of the centrifuged solution.
Robustness	System suitability criteria are met for the following method variations: Variation of organic component in the mobile phase ±5% (relative) Variation of ion-paring concentration of ±10%, when applicable Variation of mobile phase pH of ±0.1 pH units, when applicable Variation of flow rate approximately ±10% Variation of wavelength ±2 nm Variation of column temperature approximately ±5°C (where applicable)
Solution stability	The assay of the standard and sample solutions at room temperature (or refrigerated temperature) must not change by more than 5% in a specified time period at least as long as the time required to perform a typical analysis run (maximum analysis time from sample preparation should be defined in the test method).

TABLE 3.4
Validation Elements and Acceptance Criteria: Category III

Validation Elements	Acceptance Criteria
Precision	RSD is NMT 2.0%.
Accuracy	Recovery for target analyte is between 98% and 102% for spiked placebo samples at the release tolerances (Q) level.
Method linearity	These acceptance criteria must be met for a five-point concentration method range: 1. The correlation coefficient (r) is NLT 0.995. 2. The percent intercept is NLT –5.0% and NMT 5.0%.
Range	The concentration at which the precision, accuracy, and linearity criteria are met. This range should cover from the low concentration end of the stage 3 dissolution test to 120% of the drug release level.
Quantitation limit	The concentration at which the S/N ratio is approximately 10. The quantitation limit should be NMT the reporting threshold defined in ICH Q3B.
Specificity	1. No peak interference in the placebo injection at the retention time of target analyte. 2. The target analyte peak is resolved from the neighboring peaks. 3. The target analyte peak is pure by PDA analysis.
Ruggedness (intermediate precision)	1. The RSD of single determinations (injections) of six preparations under dissolution conditions (second analyst, second dissolution system) must be NMT 3.0%. 2. The RSD for the combined determinations (Analysts 1 and 2) must be NMT 5.0%.
Interference from the automated dissolution sampling system	The percent recovery for the sample collected by the auto-collector must be between 98.0% and 102.0% of the sample collected manually.
Solution stability	The assay of the sample and standard preparations must not change by more than 2.0% in a specified time period at least as long as the time required to perform a typical analysis run (maximum analysis time from sample preparation should be defined in the test method).

All deviations to the validation protocol must be documented and authorized by laboratory management and reviewed and approved by the quality assurance department. These deviations are summarized in the validation report.

Validation Planning and Protocol Execution

Instrumentation Selection

The method validation is considered as a cGMP activity, requiring that the instruments used for the validation activity be fully qualified according to installation qualification, operational qualification, and performance qualification protocols.

Standards Qualification and Handling

The standard used for the method validation must be qualified. A vendor's certificate of analysis with the purity factor is needed for establishing quantitative relationships such as relative response factors. It is preferable to use compendial standards if available for method validation. A standard qualification report is part of the requirements for questions-based review document in ANDA submission in common technical documents format.

Optimization of the Experimental Sequence for Efficiency

Validation experiments should be designed that are efficient and optimized for resource utilization.

Resources and Timelines

The number of personnel needed for the validation should be well planned. The person involved in the method validation must be trained on cGMP compliance and method validation SOPs. The timeline for the method validation should be reasonable for full documentation, for data and notebook review and signature, and for quality review and approval process. Method validations must be completed before the methods' application for API testing in pilot bio-batch or exhibit batch release.

Validation Report

The validation report is a summary of the results obtained during execution of the validation protocol. The results are compared with the acceptance criteria. The validation report must discuss whether the results pass or fail the acceptance criteria and conclude if the method is suitable for its intended use.

The validation report must also discuss and document any deviation from the protocol, justify the deviation, and analyze the impact of the deviation.

During the method validation, some parameters of the test method may be required to be modified (such as system suitability parameters) or finalized (such as relative retention time and relative response factors). These suggestions should be documented in the method validation report along with the justification for the method change.

Method Equivalency Study

When an in-house method and a compendial method exist for the same test, a comparison with the compendial monograph test method must be established to demonstrate that the in-house method is equivalent or better than the compendial method. The assessment of method equivalency can be based on statistical principles such as *F*-tests and *t*-tests or approved acceptance criteria. One lot of the finished drug product can be chosen to compare both the in-house test method and the compendial test method. The sample with multiple preparations is assayed and the results from both methods are compared. If the results pass the preapproved acceptance criteria or the statistical analysis, the two test methods are considered equivalent.

METHOD TRANSFER

After ANDA approval, the test methods will be applied to the validation batches and routine product testing conducted by quality-control laboratories. Hence, the test methods must be transferred to the quality-control laboratories. There could potentially be a difference in the geographic location of the research and development laboratory and the quality-control laboratory. The experience of the instrument operator and experience with the application of the test methods could vary from laboratory to laboratory. Therefore, the knowledge and experience must be passed to the new laboratories. The receiving laboratory must demonstrate its ability to perform the test method. A method transfer SOP or protocol must establish the requirements for satisfactory method transfer.

Objective of the Method Transfer

The method transfer is part of the technology transfer process. The method transfer can improve the understanding of the analytical methodology for both the originating and the receiving laboratories. The receiving laboratory personnel performing the test method should be trained on the test method. The receiving laboratories must be cGMP compliant. When the receiving laboratory is a contract laboratory, appropriate auditing of the laboratory by quality assurance personnel is necessary. When a method transfer (crossover) study is performed, the results from both laboratories can serve as "intermediate precision" data.

Documentation of Method Transfer

Method Transfer Protocol

To confirm that the receiving laboratory has the full grasp of the test methods, the transfer process must be documented. If the transfer process is driven by a method transfer protocol, this protocol should define the manner of method transfer, the role and responsibility of the laboratories involved, and the acceptance criteria for a successful transfer and reporting items.

One way of method transfer is by a crossover study involving both the originating laboratory and the receiving laboratories. In executing the method transfer protocol, both laboratories can test the same lot of product and the results are compared for closeness. The second way of method transfer is for the receiving laboratory to perform a mini-method validation (e.g., to reproduce the method accuracy, precision, and linearity), which demonstrates that the laboratory can fully reproduce the performance characteristics of the test method.

Method Transfer Report

Upon the completion of the method transfer protocol, the test results are summarized and compared with the preapproved acceptance criteria to determine whether the receiving laboratory is qualified to perform the test method. The transfer report should indicate whether the transfer is successful. All transfer data must be recorded and reviewed. Any deviation from the protocol must be documented and discussed. The report must include the justification for the deviation to the protocol and impact on the test method.

ADDITIONAL VALIDATION AND REVALIDATION OF THE TEST METHOD

Additional method validation and revalidation of the test method may be needed when there are regulatory changes and when the expectation for the method performance characteristics is higher. Sometimes, an alternative raw material supplier is chosen and a different impurity profile is expected due to a different synthetic manufacturing route for the API. When an old analysis technique is replaced by new techniques, method validation will be required again. The last possibility is that the validated procedure requires modification due to a discovered defect and the modified method must be revalidated, properly documented, and finally submitted as a supplemental amendment to the ANDA application.

SUMMARY AND CONCLUSIONS

Development of accurate and reliable analytical methods is an important element of pharmaceutical development. Good analytical methods support correct decisions being made from data for formulation development and stability studies. All analytical methods must be validated before they are used to generate data that will support a regulatory decision.

Analytical development can proceed efficiently if a thorough literature search is made of the available information on the API and drug product, including related compounds. A good source of information is the portion of the DMF that the API manufacturer is willing to share with its customers. When compendia method(s) is not available, then it is a good idea to work closely with the laboratory personnel from the API manufacturer in developing methods for the API and identify unknown impurities in the API.

Analytical development and validation must follow a timeline keyed to the other activities in developing a drug product. Analytical methods will usually be needed to support other plant activities such as cleaning validation or packaging development. The analytical method should be evaluated for robustness and reliability before committing the time and effort to validate a method.

A validated method can still be updated for special situations encountered during the method application. Such update may or may not involve an addendum or supplement to the method validation. This is usually part of the life cycle of the test method application.

The validation report is necessary for documenting the capability of the test method. All data that support the validation must be clearly identified and audited. These data will be scrutinized by the regulatory agency granting a drug product approval in a preapproval inspection.

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4 Experimental Formulation Development

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INTRODUCTION

The formulation scientist in the generic industry has a demanding role when developing generic oral solid dosage forms that not only need to match innovator products within tight acceptance criteria but should also circumvent restrictive formulation patents, which makes it extremely challenging to achieve the desired generic product.

As the innovator companies come under increasing pressure from generic competition, it becomes important that valuable aspects of intellectual property acquired during the development of a specific drug product be sufficiently detailed to file a formulation patent. Their primary goal is to prevent, as far as possible, generic drug products from entering the market until after the benefits of basic patent coverage and subsequent formulation patent protection have been suitably exploited. Innovator companies may also file additional patents related to the synthetic process employed to produce the active pharmaceutical ingredient (API) [1], the specific crystal form (polymorph) [2], the formulation [3], and the combination of the drug with other active(s), which might provide synergistic benefits over the specific drug administered alone [4], specific "use" patents [5], and, of late, "pediatric exclusivity" [6].

Although the literature abounds with numerous drug-product formulations, both qualitative and quantitative, it is rather surprising that formulation scientists struggle in their quest to match the innovator product from a bioequivalence point of view, resulting in failed biostudies. Possible reasons for not being able to match the innovator may well lie in the nature of the API material used [7,8], the composition of the formulation with respect to the excipients used [9,10], and the manufacturing process employed, among others [11]. Table 4.1 lists the effects of excipients on the pharmacokinetic parameters of oral drug products, clearly indicating the effect that excipients may have on bioavailability and bioequivalence [12].

TABLE 4.1
Potential Effects of Excipients on Pharmacokinetic Parameters after Oral Administration

Excipients	Example	ka	tmax	AUC
Diluents	Microcrystalline cellulose	↑	↓	↑/–
Disintegrants	Sodium starch glycolate	↑	↓	↑/–
Enteric coat	Cellulose acetate pthalate	↓	↑	↓/–
Glidant	Talc	—	—	—
Lubricants	Magnesium stearate	↓/↑	↑	↓/–
Sustained-release agents	Methylcellulose, ethylcellulose	↓	↑	↓/–

In all cases, these effects may be concentration or drug dependent.
↑ = increase, ↓ = decrease, — = no effect.
ka = absorption rate, tmax = time to peak concentration, AUC = area under the plasma drug concentration time curve.

Source: Adapted from Shargel L, Yu Y, eds. *Biopharmaceutic Considerations in Drug Product Design. Applied Biopharmaceutics and Pharmacokinetics*. 4th ed. New York: McGraw-Hill, Chapter 6, 1999:137.

It is very important to characterize the active ingredient to be used with respect to polymorph and particle size and also from a morphologic point of view. The role of particle size cannot be overemphasized, especially in APIs of decreasing solubility and permeability [13]. Failed bioequivalence studies are often due to issues of particle size, and comparatively small differences of 5 μm (or even less in some cases) in mass median diameter can spell the difference between success and failure [14]. The fact that patents concerning particle size have been filed by drug companies testifies to the importance of that parameter in formulating effective drug products [15].

Different crystal forms of the same chemical entity (polymorphs), for example, ibuprofen [16], can have varying solubilities, which could have significant implications with respect to bioequivalence if the incorrect form is used. Patent strategies pertinent to polymorph(s), provided that they are well thought-out and as far-reaching as possible, will continue to provide generic API manufacturers and formulation scientists considerable challenges. Drug manufacturers and formulation scientists have been able to counter most of the innovator polymorph strategies with considerable success, a fact that has prompted innovator drug companies to devise more elaborate patent strategies to protect their intellectual property.

The morphology of APIs is of considerable importance especially in direct-compression (dry-blending) formulations of drug products where the active content is less than 20% of the formula. Regulatory authorities the world over (especially the U.S. Food and Drug Administration [FDA]) have become increasingly aware of variations in active content in "blend samples" drawn to confirm homogeneity of active distribution after blending. In a previous report [17], lack of adequate potency and/or content uniformity was cited as the primary reason for the recall of solid dosage forms, which, from a regulatory perspective, raises the issue of whether adequate process controls (including blend homogeneity testing) and release tests are in place. Due to the fact that the active ingredient and excipients rarely demonstrate comparable particle sizes/shapes, the compositional ingredients will flow into the "collection port(s)" of a sample thief at differing rates determined by their morphology. This will often give rise to the phenomenon of blends demonstrating considerable active ingredient variation [18], whereas the resultant tablets (compressed on modern tablet presses equipped with flow optimization attributes such as force feeders) will exhibit highly satisfactory content uniformities (usually within ±5% of label claim, with a concomitantly low relative standard deviation), which easily comply with the relevant compendial requirements. Consequently, pharmaceutical manufacturers are required by law to provide evidence of the adequacy of their blending operations [19]. Regulatory authorities require that a meaningful correlation between blend uniformity and tablet/capsule content uniformity exists, despite data from several reports where blend uniformity test failures were determined to be a result of sample size, sampling errors (position and depth in blender and hopper), sample thief design, and technique of sample collection [20–22]. The formulation scientist is thus encouraged to seek creative sampling techniques to overcome sampling bias/disparity attributed to variances in morphology between active and excipient(s).

As a result of industry comment on a draft FDA guidance document [23], which has since been withdrawn, the Product Quality Research Institute Blend Uniformity Working Group published a recommendation to address the limitations with current

sampling techniques. This proposal recommends the use of stratified sampling of blend and dosage units to demonstrate adequacy of mixing for powder blends [24]. Stratified sampling involves the deliberate selection of units from various locations within a lot or batch or from various phases or periods of a process to obtain a sample. Such sampling specifically targets locations either in the blender or throughout the compression/filling operation where there is a high risk of failing content uniformity specifications.

Generally, differences observed between blend uniformity and drug-product content uniformity are less pronounced in wet granulation and compaction-type formulations compared to direct-compression formulations.

FORMULATION DEVELOPMENT STRATEGIES

Patent Search(es)

In the early days of the generic industry, once the basic patent had expired, generic pharmaceutical companies were free to launch their version(s) of the drug product(s) into the market. However, over the last 20 or so years, the innovator drug companies have sought to extend their product(s) life, focusing initially on "Process Patents" (the route of synthesis, whereby the API is produced, including any unique crystal forms that may have resulted). The synthetic pathway has been explored to the fullest and the widest possible claims have been registered. The leading generic bulk API manufacturers continue their quest to synthesize APIs that do not infringe process patents. Although generic bulk drug manufacturers were, at one time, content merely to produce non-patent-infringing active(s), many have now taken it upon themselves to file patents of their own, a ploy that considerably increases the difficulty that other raw material manufacturers will face when attempting to synthesize the same active raw material.

Formulation Patents

In certain instances, innovator drug companies have valid reasons for filing formulation patents, particularly where a specific excipient (or blend of excipients) lends a particular uniqueness in terms of release or stability [25]. However, some drug companies file patents that claim every excipient known, and such patents are clearly open to challenge.

It is more difficult to file formulation patents in the arena of immediate-release dosage forms than in the case of modified/controlled-release formulations, where creative solutions have been applied to modify the in vitro and in vivo release characteristics of active(s) to provide a dosage regimen that offers significant therapeutic advantages and improved patient compliance.

Combination Patents

Combination patents are those that pertain to more than one active ingredient combined together in a single drug product, the resultant product ideally displaying a synergistic pharmacologic response compared with each active ingredient administered on their own. One of the earliest examples of such a combination was

co-trimoxazole, where sulfamethoxazole was combined with trimethoprim. More recent examples have focused on decongestants in combination with antihistamines, for example, loratidine and pseudoephedrine, antibiotic combinations such as amoxicillin and clavulanic acid, angiotensin-converting enzyme inhibitors in combination with diuretics such as enalapril and hydrochlorothiazide or perindopril and indapamide, and antihypertensives in combination with diuretics such as atenolol and chlorthalidone.

Use Patents

In certain instances, a drug substance has been found to be of benefit in treating disorders other than those first known and recognized, for example, with omeprazole with its relatively novel indication for use in gastroesophageal reflux disease and the aminoketone antidepressant bupropion with the additional claim for use in smoking cessation. New clinical studies are undertaken to provide the additional "use" that permits the innovator company to claim that particular new indication on both label and package insert. "Use patents" prevent generic companies from making the additional claim(s) but do not prevent the generic product from being prescribed to treat conditions originally claimed in the basic patent. Consequently, "use patents" do not carry the same impact as process and formulation patents but nevertheless cannot be ignored.

Literature Search

A comprehensive literature search should be performed that focuses on the API material in question and the proposed formulation. The formulation patent(s) filed and information on the innovator's New Drug Application can be obtained by requesting the Summary Basis of Approval from the FDA at http://www.fda.gov/cder/foi/anda/ index and provides an excellent source of background information. It is essential that such a literature search be embarked upon as early in the development process as possible.

Regulatory Strategy

Once all of the patents have been comprehensively analyzed, a regulatory strategy must be formulated to establish when the "earliest date of sale" of the generic drug product can legally be made. In this respect, the Approved Drug Products (Orange) Book [26] provides useful information relating to the expiration date of appropriate patents of drug products that are the subject of approved applications but exclude process patents. The reader is referred to Chapter 15 for a more comprehensive account. Such strategies need to embrace "first to file," "exclusivity," and a whole host of "legal implications" that need to be encompassed within the project plan, which will ultimately lead to a "first to market" strategy [27]. This scenario has evolved over the past 15 years and gained prominence for the first time when ranitidine (Form 1) Abbreviated New Drug Applications were reviewed by the FDA in the mid-1990s [28].

Once patent hurdles have been fully investigated, and regulatory strategies are put in place, it is up to the formulation scientist to ensure that a non-patent-infringing

raw material can be incorporated into a non-patent-infringing formulation, which will be at least as stable as the innovator drug product and also bioequivalent (BE).

Sourcing of the Active Raw Material(s)

Purchasing an API raw material can be quite demanding and is not as straightforward as one might perceive. Databases are consulted as to which manufacturers have the required material available, and once the potential vendors are identified, each is requested to furnish the following information:

1. The detailed synthetic pathway whereby the API is produced, including all solvents, catalysts, materials, etc., utilized at every step.
2. A statement indicating that the process pathway does not infringe any patent(s) that may be in force and must be verified by the generic company's patent lawyers.
3. A statement indicating the possible polymorphic nature of the active drug in question, where relevant.
4. The batch size(s) of API, which has been manufactured to date.
5. Any validation data that may be available to provide some degree of assurance that the synthetic process has been evaluated/controlled.
6. Samples of 50 to 100 g from three discrete batches of material manufactured according to the synthetic pathway provided. In each case, the batch size should be made available.
7. A complete list of synthetic impurities and potential degradation products that may be used to fingerprint the API, together with full chemical characterization of each as well as 50 to 100 mg samples of each synthetic impurity/degradation product alluded to. Appropriate methodologies such as mass spectroscopy, high-performance liquid chromatography (HPLC), x-ray diffraction (where polymorphs may be present), nuclear magnetic resonance, and electron spin resonance, among others, are generally used for the characterization. In some instances, one of the recognized international compendia such as the United States Pharmacopoeia (USP) [29] and/or Pharmacopoeial Forum [30], the British Pharmacopoeia [31], and the European Pharmacopoeia [32] may list potential impurities and/or degradation products for the API in question. Depending on the route of synthesis followed, there may be no possibility for a listed impurity to be present in the API. Should such a situation present itself, the onus is on the API manufacturer to provide a statement as to why there is no possibility for the stated impurity to be present. Note: Such a statement would have to be supported by actually demonstrating the absence of said impurity by HPLC analysis, and in order that this be done, it is essential that the impurity be synthesized (and chemically characterized) either by the API manufacturer or by a contract laboratory.
8. A complete list of solvents used in the synthetic process (which should relate to those claimed in the detailed synthetic pathway) together with those that should be monitored in the API. Where appropriate, a statement must be

made by the API manufacturer claiming that none of the organic volatile impurities listed in the USP are present.
9. Specifications pertinent to raw material particle size, which may become better defined as the drug-product manufacturer closes in on a final formulation.
10. A Technical Package, which embraces the information requested, plus stability data to confirm suitability of the raw material in question and validated analytical methods pertinent to assay, related substances/degradation products, and residual solvents.
11. A commitment by the API manufacturer to undertake the necessary validation of the synthetic process and the batch size envisaged for future commercial production.

The vast amount of data required (not to mention the sensitivity of the information requested) will necessitate the signing of Confidentiality/Secrecy Agreements between the API manufacturer(s) and the generic pharmaceutical company. Once the information has been received and reviewed, the choice can be made as to which raw material supplier to select.

The reader is referred to the Drug Information Association Fourth Symposium on APIs held in Baltimore during November 1998 and the subsequent publication of several relevant articles in the Drug Information Journal [33–39] as well as Chapter 2 of this book.

Although the strength of the Drug Master File (DMF) or Technical Package supplied by the vendor may be the most important criterion on which to base the selection, past experiences with the bulk drug manufacturer (promptness of supply, quality, working relationships, and ability to respond to competitive pricing) should enter into the decision-making process as well.

The relationship between the API manufacturer and the generic drug company is far closer today than it ever was in the past; this is due to the considerable amount of intellectual property and strategies that need to be shared between the companies. In this respect, it is important to maintain a close liaison with the API manufacturer to ensure that any change in API manufacture is promptly communicated.

One of the most important difficulties facing both companies is the phenomenon of scale-up from R&D laboratory samples through pilot-batch manufacture to full commercial production, because it is widely known and accepted that increasing the batch size can sufficiently stress the process, thereby resulting in higher levels of impurities, residual solvents, and altered particle-size characteristics [39].

Once the exhibit batches (whose documentation is part of the submission dossier) have been produced, the API manufacturer will be in a position to file a relevant DMF with the appropriate government agency. A DMF may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of the API [40]. The information contained in the DMF may be used to support an Abbreviated New Drug Application. Any updates/amendments to the DMF must only be made after consultation with the drug-product manufacturer because such changes may jeopardize approval of the finished product. Frequently, API manufacturers will supply

drug-product manufacturers with the "open part" of a DMF, because the information therein may be necessary and useful in formulating a drug product. An open part of the DMF would typically include the following:

A. Drug substance
   - Description of API
   - Manufacture of drug substance (synthetic pathway only), which includes
     - Flow chart
     - Impurity profile
     - Demonstration of chemical structure
     - Physical characteristics of the product (spectroscopic analysis)
   - Purity of the reference material
   - Packaging and labeling

B. Laboratory controls
   - Specifications and test methods used for the API
   - Scheme of the stability evaluation protocol
   - Batch size

C. Complaints file

D. Environmental impact analysis

Alternate Vendor Sourcing

It is useful to secure approval of an alternate API manufacturer. However, different API manufacturers may have applied different strategies to overcome process patents. In such cases, there is a high probability that the impurity and residual solvent profiles will vary significantly, necessitating full analytical methods revalidation.

Where polymorphism is an issue, it is essential that both suppliers provide the identical form. From a regulatory perspective, the preferred situation would be if both manufacturers' materials were synthesized utilizing the same [very difficult to achieve if patent(s) has been filed] or a similar synthetic approach, which is likely to result in similar impurity and residual solvent profiles and polymorphic form.

The need to change sources of raw material during formulation development is unfortunately not a rare occurrence. Such situations may arise when there may initially only be a single source of supply of R&D quantities of API. Formulation development thus commences with relatively costly raw material and often, in time, additional bulk API suppliers emerge to provide raw material at more favorable prices. If the formulation scientist is required to change the raw material source for scale-up or exhibit-batch manufacture, the formulation may need to be redeveloped, because the physicochemical characteristics of the new supplier's raw material may bear scant resemblance to that used initially, and as a consequence, this may slow the project down considerably.

Even if another supplier's raw material is similar, if not identical to that employed initially, a simple substitution of the latter by the former may not result in an identical product being produced even when the raw material specifications appear identical. When faced with such a situation, it is always in the formulation scientist's best interests to undertake a series of trials, preferably at pilot-batch scale, to confirm acceptability of the alternate API from both the production and analytical points of view.

Hence, when adding an additional source or contemplating the replacement of one source of active raw material with another, all necessary precautions must be taken to ensure interchangeability and this holds true for key excipients as well.

Formulation Development

Formulation development should only commence once the following issues have been suitably addressed:

1. Relevant patents have been accessed and investigated.
2. The appropriate literature search has been undertaken.
3. Regulatory and formulation strategies have been established.
4. The desired API(s) has been ordered and received.

A beneficial approach to formulation development is to critically evaluate and, where possible, to characterize the innovator product with respect to composition, type of granulation (wet granulation or direct compression), and any other qualitative and/or quantitative analyses, which may be practical or feasible. Additional useful information relating to the innovator product may be gleaned by measuring in vitro drug release over a range of pHs and rotational speeds used in dissolution testing as well as inspection of brand labeling for stability information. Conventional microscopy and visual observation may well provide useful information regarding the granulation method used, although caution should be exercised because the results may prove inconclusive and possibly erroneous.

A simple and very useful approach is to determine the pH of the innovator drug product dispersed in a small volume of pH-adjusted purified water and then to compare the result with that yielded by a similar dispersion of the trial formulation. This approach is based on the premise that if the two dispersions provide comparable pH values, the excipient compositions of both innovator and generic formulations are probably similar. Once again, circumspection is necessary because this simple test may sometimes not be sufficiently discriminatory.

Initial trials should be undertaken employing the identical excipients referenced in texts, such as the *Physicians' Desk Reference* [41], *Compendium of Pharmaceuticals and Specialties (Canada)* [42], *Le Dictionnaire VIDAL* [43], and the *Repertorio Farmaceutico Italiano* [44].

Selection of appropriate quantities of key excipients such as binders, disintegrants/dissolution enhancers, compressibility aids, glidants, lubricants, antiadherents, and surface-active agents is an important consideration for the formulation scientist. In this regard, a valuable reference that should be consulted is *The Handbook of Pharmaceutical Excipients* [45].

It would be reasonable to presume that provided the same excipients, as outlined in referenced texts, are used, possible instability/incompatibility issues may be circumvented. However, should it be deemed necessary to use an excipient(s) not present in the innovator product, it will be prudent to evaluate such an excipient(s) for compatibility with the active ingredient using techniques such as a stability indicating HPLC assay, thin-layer chromatography, and/or differential scanning calorimetry [46,47].

It is recommended that all compression trials be undertaken, with trade dress requirements in mind, using the same punches and dies envisaged for future commercial production. This approach circumvents future compression problems such as sticking, picking, and poor friability upon subsequent exhibit-batch/commercial-batch production. In addition, it may be difficult to predict hardness/compression force settings if tooling of different dimension(s) and shape were used at development level, which in turn may affect dissolution profiles to a considerable degree [48–50].

The need to optimize tablet punch design and even consider the nature of the stainless steel used is often overlooked at the formulation stage. The fifth edition of the *Tablet Specification Manual* provides comprehensive information on specifications and quality-control programs for tablet tooling [51]. To achieve acceptable tablet compression characteristics, optimization of binder(s), lubricant(s), glidant(s), and antiadherents in the formula(s) is also an important consideration. Relatively small changes in the amount of such key excipients can dramatically alter the appearance and physical attributes of tablets, whereas the impact of such changes on drug product stability and dissolution profiles can be significant [46,52,53].

Finally, all formulation trials should be compressed on a high-speed, rotary tablet-press that is preferably instrumented [54] to provide the scientist valuable information relating to pre-compression, main compression, ejection, and take-off forces. In many instances, the API may be very expensive or in short supply. In such cases, valuable information regarding compressibility of the granule blend under high-speed conditions may be obtained by use of a tablet-press tooled with as few as four sets of punches and dies or by use of commercially available tablet presses with a small number of tooling stations.

The formulation of a capsule follows the same guidelines advocated for tablets. As was the case with the development of tablets, powder(s) intended for encapsulation can be produced by dry blending/compaction or wet granulation. Dry-blending formulations are, as the name implies, merely a blend of the active with excipients that may be included as disintegrants/dissolution enhancers, glidants, lubricants, antiadherents, surface-active agents, and diluents, where necessary. Should the powder blend need to be compacted, due care must be given to the incorporation of dry binder as well as antifrictional agents and other necessary excipients because these could have significant implications with respect to their effects both intragranularly and intergranularly. Where a wet granulation approach needs to be adopted to densify the powder, the same degree of attention regarding formulation and processing as for tablets must be adopted.

Not only is the development of a capsule formulation dependent on capsule shell size and shape, but attention must also be given to the degree of capsule fill, the quantity of lubricant to be included, as well as the type and quantity of surface-active agent used to impart improved dissolution profile characteristics [55].

The polymerization [56] of gelatin involving cross-linking and hydrogen bonding has been previously identified as a significant factor affecting the dissolution rate of active principles from solid oral dosage forms containing gelatin or encapsulated either in hard or soft gelatin capsules. The reduction in the dissolution rate may be attributed to pellicle formation due to an insoluble cross-linked portion of

the gelatin, which remains intact and can be seen by observation of the capsules in the dissolution medium. Various factors influence the dissolution rate of soft gelatin capsule shells, such as temperature, plasticizer, and various other additives [57]. This has significant bioavailability implications [58,59]. Stability and dissolution testing of gelatin-based formulations thus require special attention during product development and subsequently [60,61a,b].

Where possible, the capsule contents should fill the body of the shell as much as possible, because if too much headspace is present, the stability of the active(s) in the formulation may be compromised and susceptible to degradation reactions such as oxidation.

During the initial formulation process, it is extremely important to validate/characterize each key process, such as the following:

1. Screen sizes and milling rates (pre-granulation)
2. Dry blend mixing times (pre-granulation)
3. Quantity and rate of addition of the granulating vehicle
4. Specific granulating time(s)
5. Temperature and airflows employed during the drying process
6. Loss on drying of the granules
7. Screen sizes and milling rates (post-granulation), as well as granulometry assessment (pre-blending)
8. Times and speeds used during all blending operations, where the active granule is blended with the intergranular/extragranular phase(s)
9. All coating parameters and conditions

When the formulation scientist is satisfied with the compressibility characteristics of the formulation, aesthetic appearance, and disintegration profile of the tablets/capsules produced, samples should be submitted to the laboratory for dissolution profile testing.

The use of dissolution profile testing at the formulation development stage is extremely important, and consequently, it is essential that time and effort be devoted to developing discriminatory dissolution methods, which are sufficiently sensitive to highlight differences between innovator and test products. Caution must be exercised because it is possible to develop an overdiscriminatory dissolution test whereby dissolution rate differences between innovator and test products may not be clinically significant, suggesting bioinequivalence in cases where bioequivalence does indeed exist [62–70].

There are various approaches that can be taken to develop discriminatory dissolution methods and conditions. One process would be to determine the dissolution profiles of a drug product in a minimum of three different media, whereas another would be to devise dissolution conditions such that the active will be released gradually over a 30- to 45-min period. Matching dissolution profiles between generic and innovator products usually augurs well for future in vivo performance of the generic product. This is particularly probable for drug products containing highly soluble and highly permeable active ingredients, and if the product is rapidly dissolving, in vivo bioequivalence testing may be waived [71].

The effect of hardness on the dissolution profile must be considered for each viable tablet core formulation, and the formulation that demonstrates the least variation in release rate and extent over the widest possible hardness range (while still retaining the desired appearance and disintegration characteristics) will invariably become the "final formulation." It is this formulation and associated manufacturing process that must be scaled up in the course of further development.

Equipment Selection for Formulation Development

During the early era of generic drug product manufacture, formulation development was often commenced using different equipment to that used for pilot production, exhibit batch, and/or in the commercial-scale manufacturing facility. The process of scale-up is more often than not a daunting task even when employing equipment of the same type and operating principle during the initial stages of formulation development (small-scale) through pilot-batch (exhibit-batch) production to final full-scale (commercial) batch manufacture. As far as possible, the type of tablet compression equipment and tooling or encapsulator machinery should be identical in principle to those used for scale-up manufacture of the exhibit-batch/commercial batches, resulting in technology transfer from pilot scale to production batch occurring with few difficulties for the formulation scientist. Hence, the use of different types of equipment between the different phases of development is not recommended. A comprehensive account of scale-up and technology transfer is portrayed in Chapter 5.

Of all the processes that need to be controlled, the most critical is wet granulation because it is particularly vulnerable with respect to consistency using different types of equipment. Careful monitoring of (a) mixer and chopper speeds, (b) rate of addition of the granulating vehicle, (c) the quantity of granulating vehicle, and (d) the processing time is necessary to yield an evenly textured granulate to result in satisfactory granules after subsequent drying [72–76]. It is, however, possible to vary the type of mill used and yet achieve the desired granulometry by adroit use of screen dimension and milling rate [77].

Drying of wet granulate can be undertaken effectively using either a fluid-bed dryer or a circulating air oven, the most noticeable difference between the two techniques manifesting itself in the granulometry of the dried granule, because the fluid-bed technique tends to provide a "finer" (less dense) granule than an oven [78,79].

Wet granulation formulations tend to suffer less from nonhomogeneity of (active) distribution than do direct-compression formulations, because the active/excipients are far more intimately mixed before granulation than can be effected by traditional dry blending. Each granule yielded by wet granulation should thus comprise a homogenous blend of active and excipients, whereas, in the case of direct-compression formulations, the blending is far less vigorous and the materials being blended are usually not of the same size and morphology, these two differences being the main contributing factors to dry blends demonstrating greater (active) variation than those produced by wet granulation [80].

The type of blender used can also affect the compressibility and, to a lesser extent, the encapsulation characteristics of a granule/powder blend. Blenders that offer too intimate a mix between granule and intergranular excipients (as in the case of wet

granulation formulations) can result in granules for compression that provide tablet cores demonstrating

- Prolonged disintegration times (due to excessive hydrophobic layer build-up because of "overblending" with hydrophobic lubricants such as magnesium stearate) [81]
- Low hardness, which again is a symptom of too intimate a contact between granule, lubricant(s), and some intergranular disintegrants

The selection of blender and blending times can also impact the final granule with respect to active/excipient homogeneity and compressibility [17]. In the case of direct-compression formulations, overblending can result in demixing of active [82], in addition to prolonged, disintegration times and soft tablets [83]. Similarly, underblending can give rise to homogeneity and compressibility/encapsulation problems. Consequently, the formulation scientist must optimize the blending conditions during formulation development, with the realization that these may well vary from product to product.

Many pharmaceutical companies employ a perforated pan (e.g., Accela-Cota) coating system to film coat tablets. Sugar coating has almost entirely been eclipsed by film coating. Once again, it would be in the company's best interests to ensure that the formulation scientist is provided with a smaller version [12- or 24-inch pan(s)] of the same equipment used in the production facility. In addition, environmental, safety, and cost concerns have necessitated the change to aqueous-based film-coating dispersions or water-soluble polymers from organic solvent–based coating solutions. However, the use of organic solvents may, in certain cases, be unavoidable.

Assessment of the Final Formulation and Exhibit-Batch Production

The most promising formulation, selected based on consistent/satisfactory in vitro drug release over a broad hardness range, is then scaled up from an initial development batch size of 5000 units to approximately 20,000 units. Samples of the drug product (which may be in the form of uncoated/coated tablets or capsules) are then packaged in all possible configurations intended for future commercialization, and placed on "informal stability" (investigative stability assessment) together with the appropriate packaging(s) of innovator product, both of which have been analyzed for potency, degradation products, and dissolution profile. By so doing, it is possible to evaluate the comparative stability of the generic product against the product of original research.

"Informal stability" is carried out under "accelerated" conditions of elevated temperature/humidity (normally 40°C/75% relative humidity [RH]) and light (where applicable) for a period of 2 to 3 months. It is also useful to place the Reference Listed Drug (RLD or Brand) on accelerated stability. The generic product is analyzed at monthly intervals for active content/potency, and related substances/degradation products and dissolution profiles are generated. Should stability problems manifest with the generic product stored under a specific storage condition, then testing of the RLD stored under the same conditions can be extremely informative.

It is preferable to analyze the samples using validated analytical procedures because those would be the analytical methodologies employed during full stability evaluation of samples derived from the exhibit-batch manufacturing program.

Should the generic product prove to be stable over a 2- to 3-month period of exposure to accelerated conditions, there would be a high degree of probability that the formulation scientist has succeeded in formulating a stable drug product.

It is also vitally important to ensure that all desirable characteristics observed during the manufacture of the final formula at development level are maintained as closely as possible when the formulation is scaled up. The dissolution and disintegration profiles at the predetermined hardness levels (where applicable) should be consistent. The bulk and tapped densities of the powder/granule, before compression/encapsulation, as well as the pertinent granulometries should be similar and the "loss on drying" values of the granule/powder before compression/encapsulation should be consistent with previous data.

Once the generic drug product has demonstrated a minimum of 2 months of satisfactory stability, attention must be focused on the following:

- Development of specifications for both raw material (API) and the dosage form
- Ordering of the API and excipients for exhibit-batch manufacture
- Ordering of all relevant tooling, change parts, and capsule shells (if required)
- Completion of a Development Report

It is essential that the raw material specifications are set in conjunction with the API manufacturer to avoid setting specifications that may be considered too restrictive by the latter. The debate invariably involves limits with respect to related substances/impurities/degradation products, residual solvents, particle size, and, in certain instances, microbial limits, especially where the active raw material(s) is produced by fermentation at some stage during the synthetic pathway. Only once both parties are in full agreement should the requisite specification(s) be confirmed and signed by the responsible persons.

Development Report

A Development Report is a summary of the complete development process and will be the subject of keen regulatory agency scrutiny during a Pre-approval Inspection (FDA) or any other similar audit.

This report must make detailed reference to the following:

a. An overview of the actions and uses of the particular active as well as any information pertinent to the relevant pharmacokinetics.
b. A brief description of the innovator product and the pack sizes commercially available and appropriate to all markets where the product is destined to be sold.
c. A detailed summary of the innovator product's physical characteristics (such as appearance, size, shape, and weight). The inclusion of a photograph, as visual confirmation, is desirable.

d. A comprehensive account of the APIs used during the formulation development process, including sources of supply. All information pertinent to the polymorphic form used in development compared with that used by the innovator (which is usually easier to determine in drug products containing more than 25% of active) as well as particle sizes of the APIs, bulk/tapped densities information, and the mechanism whereby the appropriate specifications were established. Generally, three lots of API from an approved supplier should be analyzed, and based on the resultant data, specifications need to be set. Compendial monograph(s) may be too lenient as far as impurity limits are concerned, and often, data relating to residual solvent presence, particle size, polymorph, and polymorph ratio are either absent or scant.
e. A section dealing with the development of a discriminatory dissolution method, including profiles of the generic and RLD product(s) using this method and conditions. The dissolution methodology outlined in the USP, British Pharmacopoeia, or European Pharmacopoeia may not be sufficiently discriminatory to serve formulation development needs. Because the particular compendial method serves as a "batch release" specification for the commercial product, it is essential that both the innovator and generic drug products meet applicable compendial specifications.
f. A detailed account of all experimentation undertaken to arrive at the "final formulation." Reference should be made (ideally in the form of an "Appendix") to each formula employed, details of granulometries, bulk and tapped densities, loss on drying, and ranges of tablet core hardness together with associated disintegration times and dissolution profiles.
g. A detailed account of all experimentation undertaken to prove
    - "Ruggedness" of process (investigating such effects as "under" and "over" granulation, "over" and "under" blending, the impact of varying the screen size[s], and milling rates during the comminuting process[es], etc.)
    - "Ruggedness" of formulation (by varying the percentages of all "key" ingredients as permitted by the SUPAC [84] "level 1" change) and a comparison of all "trial" formulations to a "control" (the derived "final formulation") with all batch sizes identical to those produced at the formulation development stage.

    Instead of varying excipient ranges at the level advocated by SUPAC "level 1" change, many formulation scientists prefer to investigate the effect(s) of raising and lowering the percentages of all key excipients by 20% of their level in the final formulation because this is thought to provide more meaningful data reflecting the robustness of the formulation.

    Only where the coating confers some functionality to the formulation (controlled or delayed-release) need the coating levels be varied as detailed above.

    For each trial formulation, only the pertinent physicochemical attributes need be assessed, such as content uniformity and dissolution profile, the latter employing a discriminatory dissolution method.
h. An account of the formulation(s) to be progressed to exhibit-batch level as well as a brief outline of the desired manufacturing pathway.

Master Manufacturing Document

This document must be drawn up by a team comprising the formulation scientist and his/her counterpart in the exhibit-batch manufacturing section. Once agreement has been reached, a draft of the "Master" document is forwarded to Plant Operations for comment and acceptance.

A copy of the signed Master Manufacturing Document is then provided to the Process Validation Department for generation of the Process and Cleaning Qualification protocols. In general, the validation process requires at least three batches of each strength of drug product to be assessed, whereas the qualification process relates to a single batch of each strength of drug product only.

The Process Qualification Protocols must monitor and control all key processes in the manufacturing pathway such as the following:

- Volume and rate of addition of granulating vehicle
- Exact drying conditions
- Milling rates, screen sizes, etc.
- Blender rotation speeds and mixing times
- Blend uniformity after blending
- Blend uniformity after discharge of the granule into "holding bins" (to evaluate if active segregation has resulted on discharge)
- Granulometry assessments, bulk and tapped density determinations, and loss on drying measurements before and after granule discharge from the blender

Before compressing the batch of granules into tablets at the optimum hardness and speed, the following parameters need to be established:

a. "Low" and "high" hardness levels at which the tablets can be compressed meeting all predetermined acceptance criteria, with specific reference to dissolution profiles.
b. The highest speed at which the particular press can be operated to provide tablets meeting predetermined acceptance criteria, with specific reference to content uniformity.
c. Humidity and temperature (these are controlled in plant operations by standard operating procedures, whereas specific conditions are imposed by product-specific demands during formulation development).

Samples must be drawn at predetermined intervals during the compression cycle and then grouped into sets reflecting the beginning, middle, and end of the run. Samples from each stage must be tested for assay, content uniformity, and dissolution profile in addition to full physical characterization (hardness, disintegration, friability, average weight, individual weights, etc.).

A Qualification Report embracing all the results must be completed once the batch(es) has been manufactured and the analyses have been completed.

Once the specifications have been set, the API and excipients ordered, received, and tested, the necessary tooling received and verified, the Development Report

written, the Master Manufacturing Document approved and signed off, the Process and Cleaning Qualification protocols written, and the third month's satisfactory informal stability results (which indicate drug product stability) generated, the exhibit-batch manufacture can be progressed.

Exhibit-Batch Production

Manufacture of the exhibit batch is the responsibility of the formulation scientist/technician(s) associated with the development of the final formulation together with the scale-up or "technical transfer" team. The formulation and process should be tested by manufacturing a subbatch using similar equipment as the scale-up equipment and using the same raw materials intended for exhibit-batch manufacture. For example, using a 15 kg capacity granulator, consider the need to manufacture 150,000 × 500 mg tablets (i.e., 75 kg batch size). In this case, five granulation sublots would be required (75/15 = 5) to complete the batch manufacture. Hence, one sublot or more can be used to optimize the granulation parameters, and once this has been done, these parameters are applied to the actual exhibit batch. In so doing, the granulation, drying, milling, and blending operations can be optimized in advance, thereby obviating the possibility of problems occurring during subsequent batch production.

This preliminary sub-batch must be progressed to completion and samples must be submitted to the laboratory to confirm both physical and chemical attributes of the dosage form. Only once the testing has revealed an acceptable comparison with the development batches produced to the same formula and process should the actual exhibit-batch manufacture be undertaken.

Clearly, all exhibit-batch manufacture is required to be carried out under current good manufacturing practice (cGMP) conditions [85].

Samples from the exhibit batch must be submitted to the laboratory, and only when the predetermined acceptance criteria have been met (imposed at both "Batch Release" and "Process Qualification" levels) can the generic product be randomized and subsequently packaged.

Randomization is required so that any bias in the manufacturing process is removed. This involves blending a batch of drug product in a blender of sufficient size, for example, a "drum roller" blender, following validation of the process. Validation involves the addition and mixing of an equal mass of tablets/capsules of the same size but different colors (red and blue, for example) and their distribution is evaluated after rotating the blender for a set number of revolutions. The process may be deemed to be validated if, after three consecutive tests, the different color drug products are uniformly distributed with approximately ±20% variation in the samples drawn (usually 100 units). For example, draw ten 100 tablet samples of the blended lot of red and blue tablets to characterize the blending process. Determine the number of red and blue units in each sample. Acceptable randomization would thus be 30:70 (red/blue) or 70:30 (red/blue). In the case of coated tablets, the rotation of the coating pan automatically confers acceptable randomization on the coated tablets.

Before packaging of the batch(es), the necessary Packaging Documentation needs to be prepared. This describes the actual packaging disposition of each batch. It is customary to package each batch (in its entirety) into equal quantities (taking the actual batch "yield" into account) of each packaging configuration to be utilized after initially removing sufficient quantity for "large pack" evaluation under controlled warehouse conditions. For example, if 50,000 tablets/capsules are removed for "large pack" evaluation, the balance can be packed into various sizes such as 50s, 100s, 250s, 500s, and 1000s. Each of the container closure systems must be of identical material/chemical composition as the large storage container for the 50,000 batch. The packaging operation must be carried out under cGMP conditions using large-plant equipment.

Once the product has been packaged, samples of each pack size are incorporated into formal stability programs (usually 40°C/75% RH, 30°C/65% RH, and 25°C/60% RH) [86,87] according to a Stability Protocol, which outlines the pack sizes and types to be evaluated, the manufacturer(s) of the packaging components and actual composition thereof, the predetermined times at which samples must be drawn, the necessary testing that needs to be undertaken, and the predetermined acceptance criteria that are required to be met. Refer to Chapter 6 for further details on stability testing and stability protocols.

Drug product(s) containing APIs sensitive to light should be tested in appropriate photostability chambers according to an approved protocol. Samples of innovator product(s) should be included as controls for each accelerated condition specified.

It is generally considered that the formulation of tablets is somewhat more complex than capsules; hence, the manufacturing processes required to produce tablets are necessarily more rigorous than those required to manufacture capsules. The foregoing processes have thus focused on the development of tablet dosage forms, while at times occasional references were made to capsules. Nevertheless, similar considerations apply to the development of a capsule dosage form.

Appendices A4.1 and A4.2 are provided herewith to outline the processes and sequences involved in the development of a generic tablet dosage form.

Quality-by-Design Approaches

The introduction of the concept of "Quality-by-Design" (QbD) marks a fundamental shift in the drug product development process. The FDA cGMP document envisioned a modern, efficient, and flexible pharmaceutical manufacturing sector for the 21st century to ensure the reliable production of high-quality drug products without the need for extensive regulatory oversight [88]. However, the drug product development approach commonly used by industry relies on empirical formulation development followed by postmanufacture testing of the quality of the dosage form. Therefore, the goal of the FDA was to address major issues related to the state of pharmaceutical manufacturing, such as the inability to predict the possible effects of scale-up on the final product, inability to analyze or understand reasons for manufacturing failures, and the achievement of reasonable product quality at a great effort and cost, among other issues. After a decade, this goal is still a challenge for most pharmaceutical companies. However, the FDA will require that companies in

the future must submit data, which support specifications and justify the upper and lower limits thereof.

The most appropriate way to achieve the requisite outcomes and regulatory goals and be compliant with regulatory challenges in the future is to apply QbD approaches in drug product development and manufacturing. This concept is, as previously mentioned, a fundamental shift from the former traditional outlined formulation approach. Traditional formulations were developed partially or entirely from empirical knowledge and/or some statistical approaches such as design of experiments (DoE). If the created dosage form seemed to be appropriate, for example, the hardness of a tablet was suitable, then the overall quality and specifications of the new formulation were defined for the formulation using a variety of tests including disintegration and/or dissolution tests [89–93].

In QbD, the goals and specifications are normally set before any experiments or before formulation work is performed. The so-called Quality Target Product Profile (QTPP) is essentially the vision for the final product, its route of administration, container type, desired pharmacokinetics, and associated critical quality attributes (CQA). This initial design has to be based on existing knowledge. Therefore, a large as possible knowledge base is needed to put the formulation strategy together. Many excipient suppliers provide comprehensive information about their excipients, which can be used in QbD approaches during the early design stages [94].

Another goal of QbD is to identify risk, control processes, and test variability and to establish a control and improvement strategy throughout the lifecycle of a product. Knowledge of the impact of variability on the performance of a drug product then enables the formulation scientist to create and define a design space (DS), which subsequently must be confirmed by experimental approaches. A sufficient understanding of the variables that need to be controlled within the DS will facilitate the development of the control strategy [95].

QbD approaches can be implemented using International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines Q8 (Pharmaceutical Development) [96], Q9 (Quality Risk Management) [97], and Q10 (Pharmaceutical Quality System) [98]. ICH Q8 defines DS as a multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality and process understanding [96]. Changing parameters within the DS is therefore not considered as a change and does not require any regulatory approval for such modifications. The entire DS is approved as part of the new drug application. This means that the DS creates an opportunity and flexibility for a risk-based manufacturing process that can subsequently undergo continual improvement without regulatory approval for the adjustments that are made (Figure 4.1). Any changes to process or product that fall outside the approved DS, or changes not described in the drug product dossier, will require further regulatory review. The major advantage that QbD offers over a conventional product development approach is that there is the potential for a significant reduction of postapproval submissions. The quality system designed around a product ensures consistency and allows improvements without regulatory review and approval. Another important consideration is that QbD allows the possibility of real-time quality control, leading to a possible reduction

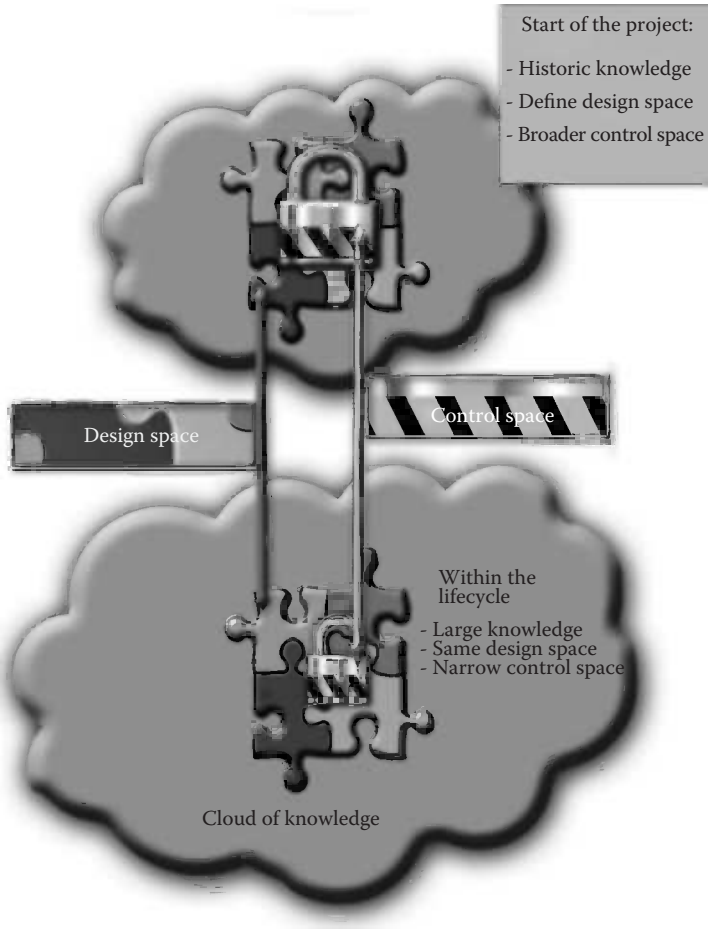


FIGURE 4.1 QbD and the lifecycle of a product.

or even elimination of endproduct release testing [99]. Because QbD is a systematic approach to pharmaceutical product development, it is important to understand the steps of designing and developing formulations and manufacturing processes to ensure that the predefined product quality is achieved [100].

The API and all manufacturing processes necessary to produce an acceptable formulation are key elements for the performance of a drug product. Both API and processes must be considered in a QbD environment. Therefore, mechanistic knowledge of the Biopharmaceutical Drug Classification System (BCS) [101] is a useful starting point to characterize an API when designing a formulation. However, the BCS class of an API has to be put into the context of the dosage form. Additional considerations such as the dependence of dissolution, dose, and absorption time on the bioavailability of a drug are essential. The BCS defines these parameters as Dissolution Number, Dose Number, and Absorption Number [101]. Modern software packages can use

these numbers to model oral absorption. If, for example, the Dissolution Number of a drug is too low, then the formation scientist can increase API dissolution by milling the API or apply other dissolution enhancing technologies to optimize this parameter. Additionally, solubility-enhancing technologies such as the use of surfactants in a formulation might move a drug's biopharmaceutical behavior from a low solubility class to a high solubility class; however, this will not change a drug's BCS class while it might change its biopharmaceutical behavior. On the contrary, if the Absorption Number of a drug is found to be insufficient, then formulation approaches such as increased dissolution or solubility will not improve a drug's bioavailability. This basic knowledge of the BCS can be used to ensure that a sound and robust formulation is developed and that the performance is guaranteed when used in a QbD setting.

Figure 4.2 depicts two different scenarios in oral drug absorption, viz., (a) permeability controls drug absorption as so often happens for BCS Class 1 and 3 drugs, and (b) dissolution controlled absorption as expected for some BCS Class 2 and 4 drugs.

In Figure 4.2a, a reference profile is shown in addition to the minimum dissolution profile that is required to ensure bioequivalence. Any formulation that exceeds the minimum dissolution should therefore be BE to the reference product because the process is permeability controlled; any increase beyond the minimum dissolution rate has no impact on BE. In this example, only a lower limit of dissolution is required to ensure BE. Computer simulations can be used to define the particle size requirements that are necessary to stay within the dissolution requirements to achieve BE.

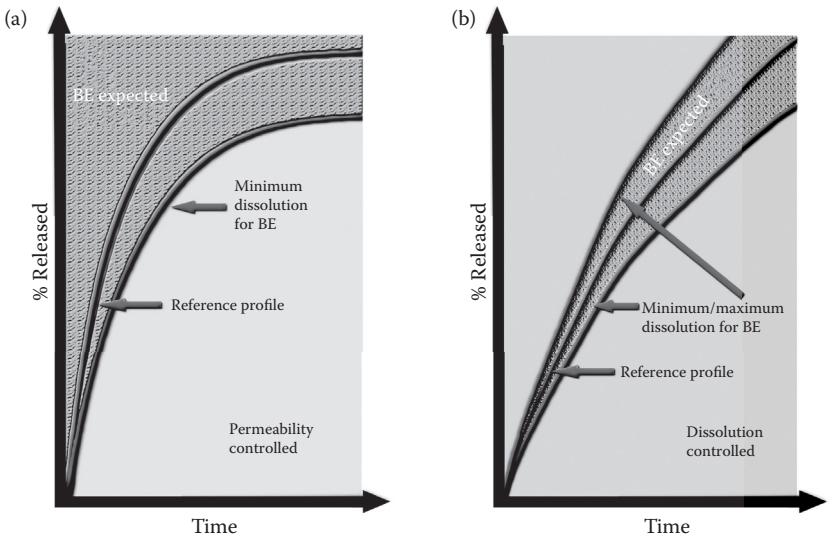


FIGURE 4.2 Dissolution requirements for oral drug absorption that is (a) permeability or (b) dissolution controlled.

Figure 4.2b depicts a reference profile and upper and lower limits of the API dissolution that will ensure bioequivalence. If an API has a wide particle size distribution or is not monomodally distributed, then a shift from permeability to dissolution-controlled absorption might be observed throughout the entire absorption process. In such cases, all the small particles will initially dissolve rapidly, after which slow dissolution of the larger particles will occur. If the dissolution of these particles takes longer than the absorption of the already dissolved fraction, then the process of drug absorption switches from permeability-controlled to dissolution-controlled absorption. Such knowledge is extremely important to be able to set meaningful API particle size and size distribution ranges and to justify the selected particle size specifications. These examples demonstrate how knowledge of the BCS characteristics of an API and the mechanistic knowledge of the absorption process can be used to identify CQAs of a dosage form.

An example of how computer simulations can assist in formulation development and particle size specifications has been described by Wei et al. [102]. The authors showed that GastroPlus (Simulations Plus, Lancaster, California), a physiologically based simulation software package, was able to predict the pharmacokinetics of glyburide. The simulation was performed using API particle size and size distribution as key parameters for the simulation. This case study demonstrates that API specifications can be set if an in vitro/in vivo correlation (IVIVC) is established between physicochemical API characteristics and the oral performance of a drug product. In a QbD environment, such an IVIVC might be used to define and justify a DS for particle size and size distribution.

There are a number of essential elements that are commonly used in any QbD strategy. Initially, the process commences with the outline of a QTPP. At this point, the prospective and dynamic quality characteristics of a drug product are defined to ensure that the desired quality, safety, and efficacy of the drug product can be realized. To achieve this prior knowledge, BCS classification of the API and the body of scientific information and data about existing products and their processes are used. The next phase is to identify CQAs, which can include physical, chemical, biological, and/or microbiological properties or other characteristics that need to be controlled (directly or indirectly) to ensure that product quality and performance are achieved. As outlined above, the particle size of the API or dissolution requirements of the product may be CQA. The definition of CQA also requires the establishment of Critical Process Parameters (CPPs). Manufacturing process parameters have certain associated variability that may impact one or more of the previously defined quality attributes. If control within a process is established and maintained, it is anticipated that the process will produce products of the desired quality. It is important to note that a CPP remains critical even if it is a well-controlled parameter. Furthermore, the product is designed to meet the needs of the patient and performance requirements defined by the CQA for that product [103].

Well-controlled CPP and knowledge of the impact on product performance together with statistical analysis enable the QbD team to define the borders and limitations of the DS for that product. Statistical analysis can assist in defining a DS in the early stages of the product and process development in addition to the final DS. DoE is a powerful tool for determining the impact of multiple variables and their

interactions on processes by revealing possible relationships between the factors that affect a process (independent variable) and the responses that are evaluated as a consequence of the process (dependent variable) [104]. Such knowledge can then be used to define a Control Strategy and to distinguish between critical and non-critical parameters. In this case, the input material controls, process controls including Process Analytical Technology (PAT), or process monitoring data and finished product tests (if appropriate) are combined to establish and ensure product quality. Finally, Quality Risk Management is defined for the product and is used to systematically assess the risks associated with all processes and controls with the goal to minimize risk to the quality of the drug product throughout the lifecycle of that product [103].

Figure 4.3 illustrates a hypothetical process for the manufacture of paracetamol (acetaminophen) tablets produced by wet granulation using a fluidized bed process. The aim of this example is to optimize fluid-bed granulation and tablet compression processes using a DS approach. In the first process, the powder to be granulated is suspended in heated air within the fluid-bed drier and the liquid binder is sprayed from nozzles located at the top of the chamber.

The use of risk analysis (Failure Mode and Effect Analysis [FMEA]) helps to decide what parameters are important to evaluate in the process. The FMEA defines the following CPP for this fluidized bed process, viz., the atomization pressure used in the fluid-bed granulator system. The second process involves compression force used in the tableting machine. The CPPs are shown to influence the dissolution rate profile of paracetamol that is a CQA, which will impact the efficacy of the final product. The CPPs were evaluated in the range between 3.50 and 4.00 kN for the compression force and between 0.50 and 1.00 bar for the atomization pressure. The

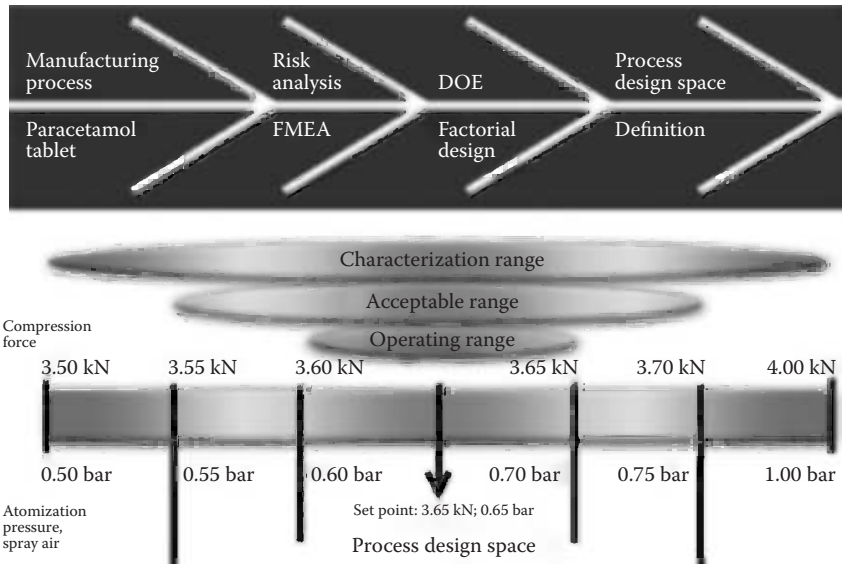


FIGURE 4.3 Steps for defining the design space process.

relationship between atomization pressure, compression force, and the CQA can be established using factorial design (DoE). This approach allows for the control of the CPP within predefined limits to ensure that the product meets predefined specifications (e.g., percent paracetamol released >80 in 30 minutes or Q = 80% in 30 minutes). The acceptable ranges for the CPP were found to be 3.55 to 3.70 kN for the compression force and 0.55 to 0.70 bar for the atomization pressure. The operational ranges were set within the acceptable ranges of 3.60 to 3.65 kN for the compression force and 0.60 to 0.70 bar for the atomization pressure. The acceptable range is consequently defined as the DS for this process. This range is revealed by Figure 4.4, a surface response plot, generated by the statistical analysis using DoE. The region, in the figure, that provides the percent (w/v) release of paracetamol higher than 80 corresponds to the DS.

Lourenço et al. [105] showed another successful example of QbD/DS application for a granulation process using a Central Composite Design scheme. The design was composed of three factors, five levels, and six repetitions of the central point totaling 20 experimental runs. The factors tested included inlet air temperature, airflow rate, and binder spray rate during the spraying phase of granulation. The mixing and the drying phases were kept constant. The study revealed that the granules with the best flow properties were produced with moisture content at the end of the spraying phases of between 12% and 16% (w/w). The results allowed optimization of the process and it was possible to generate a DS between the values of 12% and 16% (w/w) moisture. The DS provided a wider range within the moisture content that can be varied during future manufacturing without the need for additional regulatory approval. These examples show how QbD can be used in manufacturing to define and use a DS.

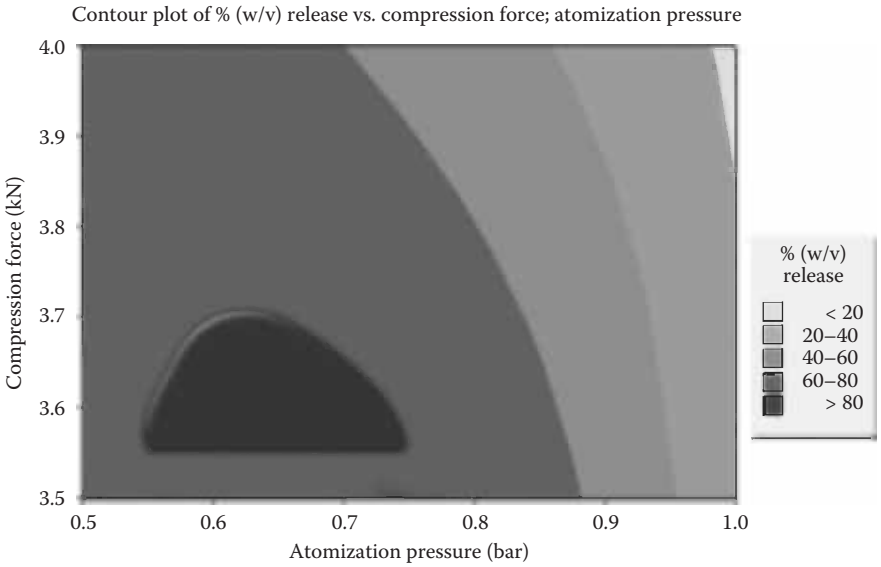


FIGURE 4.4 Percentage (% w/v) of paracetamol (acetaminophen) released changing as a function of independent variables (atomization pressure and compression force).

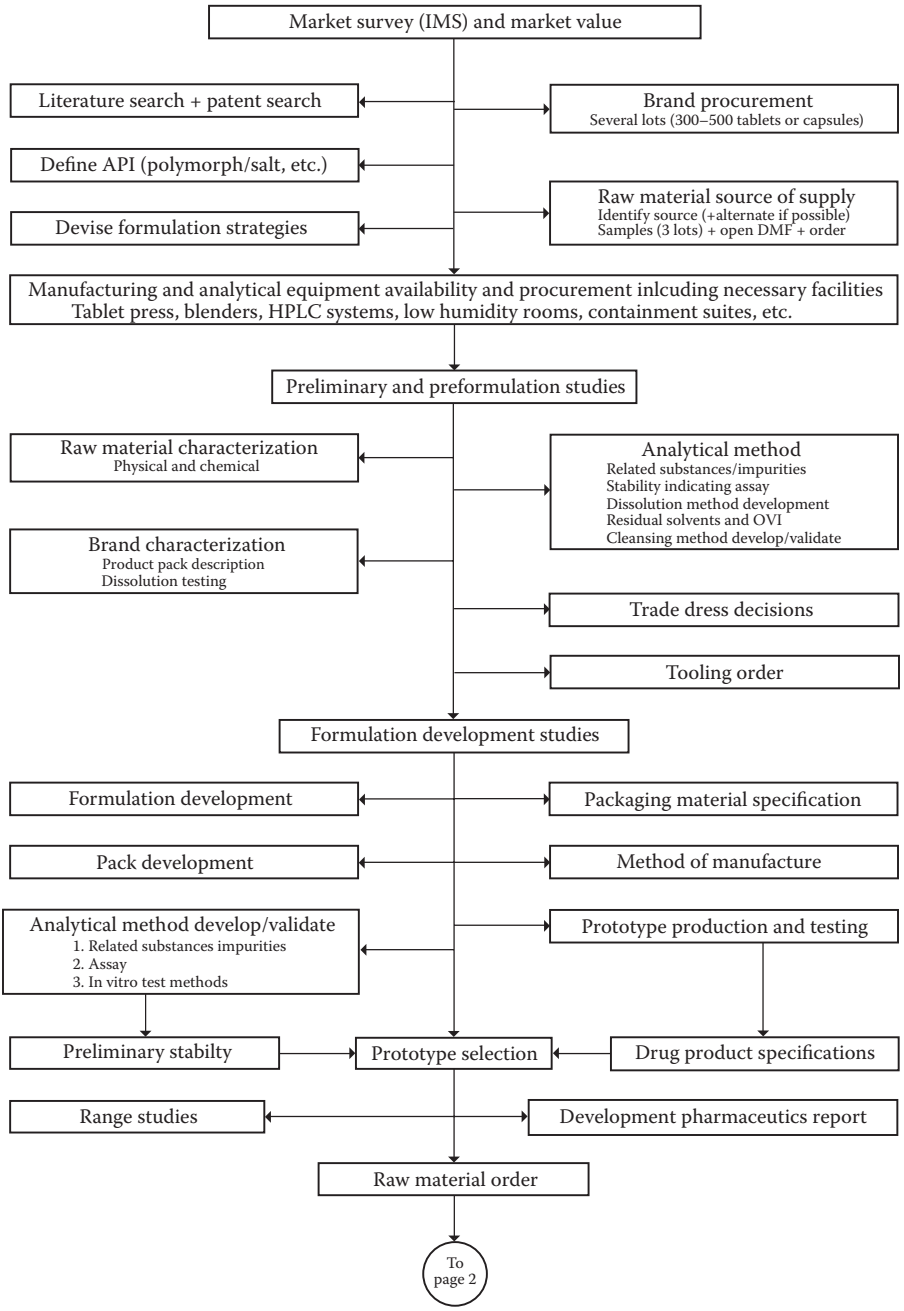
The concepts of QbD and PAT were developed at about the same time. PAT is defined according to ICH Q8 as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of CQA and critical process attributes of raw and in-process materials and processes with the goal of ensuring final product quality. PAT, as a monitoring tool at the industrial scale process, allows for the development of quantitative methods for real-time prediction of CQA. Near-infrared and Raman spectroscopy using univariate and multivariate data analysis and information management systems are among the most common tools applied to PAT to understand, optimize, and control manufacturing processes [106,107]. Considering that all manufacturing and measurement processes exhibit a certain degree of variability, PAT associated with quality assessment and statistical tools can help understand the sources and detect the presence and degree of variability, help understand the impact of variation on the process and ultimately on CQA, and control variability in a manner commensurate with the risk it represents to the process and product, as required by the FDA [108].

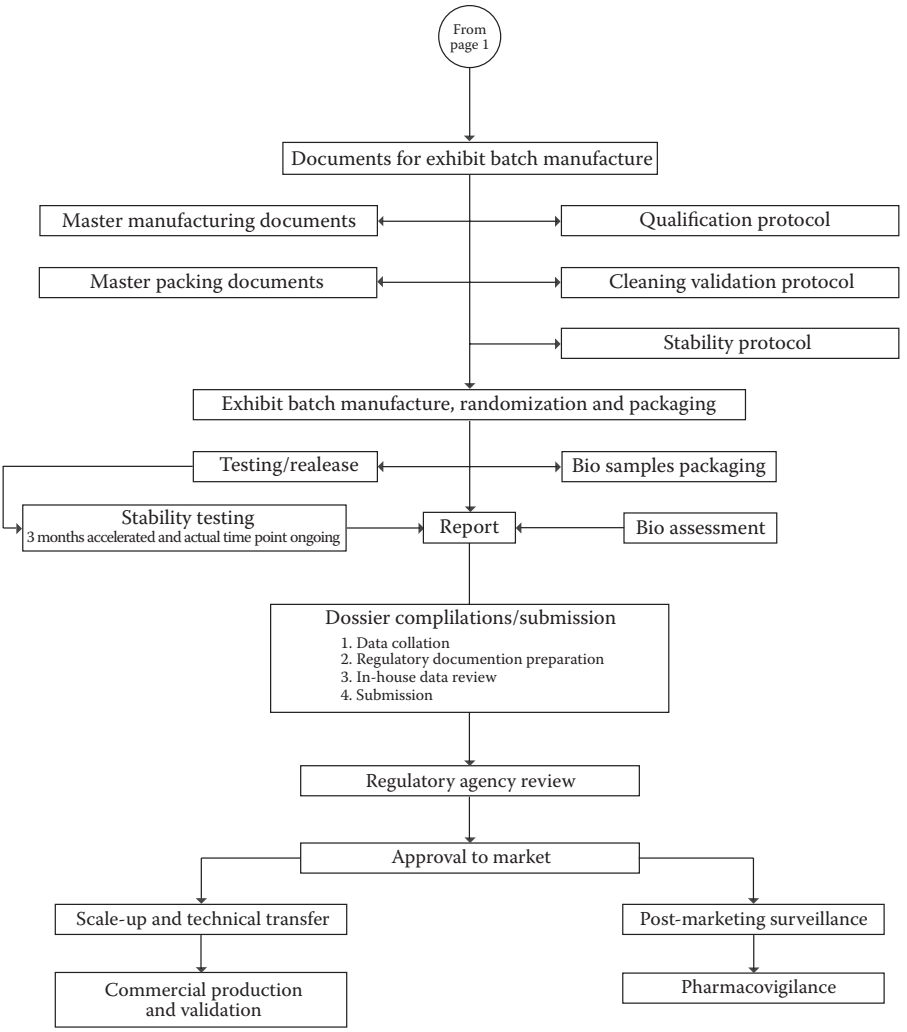
The aim of process evaluation/validation in QbD is to gain understanding of variability that might be characterized by a pattern that changes over time and appears to be unpredictable. Controlled variability is characterized by a stable and consistent pattern of variation over time and can be determined by use of Statistical Process Control Charts. The use of statistical tools can enhance process understanding and foster innovative approaches to process validation and pharmaceutical development. The absence of variation created by a nonrandom event (special causes) indicates a stable process. By evaluating the process capability indices (i.e., Cp and Cpk), it is possible to measure the ability of a process to manufacture products that meet the specifications and requirements set for that product. The Cp measures how close a process is running to its specification limits, relative to the natural variability of the process. The Cpk measures how centered the output of the process is between its lower and upper specification limits and how variable (how stable or nonstable) the output is. These indices greatly simplify the management of statistically controlled processes and have been used with the fundamental assumption that the data are distributed normally, the process is stable, and the variability is known [109,110].

QbD, PAT, and process validation are complementary strategies addressed in ICH Q8 [96], ICH Q9 [97], and ICH Q10 [98] as well as cGMP guidelines, the Process Validation Guideline, and the Quality Systems Approach to Pharmaceutical cGMP Regulations. The objectives are similar and the language is consistent [111, 112]. However, QbD is a much more comprehensive approach compared with PAT because it captures the entire product and the associated lifecycle. PAT monitors only one process and is a tool that might be used within a QbD approach.

Quality system approaches to cGMP regulation, as well as risk management adoption, are expected to encourage the pharmaceutical industry toward innovation, product quality consistency, and regulatory flexibility. Accordingly, the quality of the product must be built in from the design and development phase and throughout the lifecycle of that product. The goal is to ensure that a product of predefined quality is always produced at the end of a process. By increasing the scientific understanding of products and processes, QbD makes risk-based compliance possible and allows the pharmaceutical industry to manufacture products with greater flexibility without compromising quality or performance.

APPENDIX 4.A1: PRODUCT DEVELOPMENT FLOW CHART




From page 1
Documents for exhibit batch manufacture
Master manufacturing documents
Qualification protocol
Master packing documents
Cleaning validation protocol
Stability protocol
Exhibit batch manufacture, randomization and packaging
Testing/realease
Bio samples packaging
Stability testing
3 months accelerated and actual time point ongoing
Report
Bio assessment
Dossier complilations/submission
1. Data collation
2. Regulatory documention preparation
3. In-house data review
4. Submission
Regulatory agency review
Approval to market
Scale-up and technical transfer
Post-marketing surveillance
Commercial production and validation
Pharmacovigilance

APPENDIX 4.A2: DESCRIPTION OF THE FORMULATION-DEVELOPMENT AND SUBSEQUENT EXHIBIT-BATCH MANUFACTURE OF A GENERIC SOLID ORAL DOSAGE FORM (TABLET)

Acquisition of API and Technical Package Following Comprehensive Literature and Patent Reviews

A full set of all specified impurities together with a characterized working reference standard and a list of residual solvents must be included with the Technical Package (which is also known as the Open DMF).

Preformulation Studies on the API

a. Appearance and color (e.g., a white crystalline powder)
b. Polymorphism differential scanning calorimetry/differential thermal analysis (DTA); infrared and x-ray diffraction; tests to confirm identity and, in some cases, the ratio of the desired polymorph-mix
c. Solubility in various solvents including water
d. Particle-size determination

It is advisable to set an in-house particle-size specification, which is then submitted to the supplier describing the method used. A relevant specification can then be set in collaboration with the supplier. A three-tier specification such as those initially adopted by the Canadian TPD and subsequently by various European Regulatory Agencies, FDA, and, more recently, the Australian Therapeutic Goods Administration is recommended.

A typical specification is described hereunder:

$$d(0.9) \leq 60\ \mu m;\ 10\ \mu m \leq d(4.3) \leq 25\ \mu m;\ d(0.1) \geq 2\ \mu m$$

which indicates that 90% of the particles are less than/equal to 60 mm; the "volume mean" lies between 10 and 25 mm, whereas 10% of the particles are greater than/equal to 2 μm. By setting a three-tier specification as outlined, the normal "bell-shaped" distribution curve is implied.

Innovator Product Characterization

a. Qualitative composition refer to all available sources of information (e.g., *Physicians' Desk Reference* and *Compendium of Pharmaceuticals and Specialties* [Canada] from which relevant information can usually be obtained).

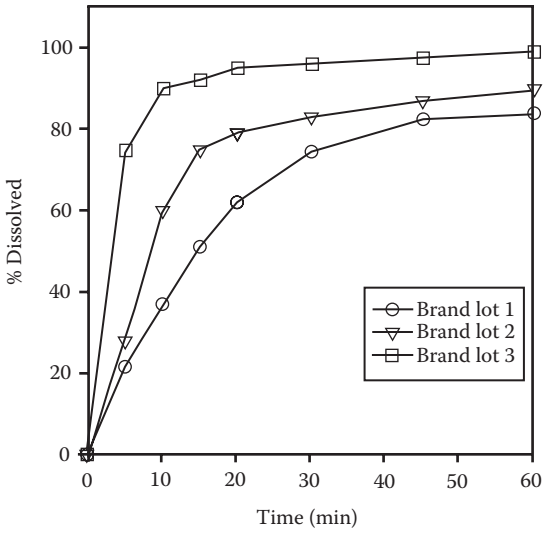


FIGURE 4.5 Comparative dissolution profiles of three different brand lots of the same commercially available product.

b. Comparative dissolution rate studies should be conducted on several different lots of commercially available product using an appropriate method (Figure 4.5). Dissolution test methods should be adequately discriminatory to identify true differences in dissolution rate and extent, if and where they do exist. Compendial methods (if shown to be discriminatory) are preferable.

Formulation Development

Formulation development is undertaken on comparatively small batches between 2000 and 5000 units. Physical data are captured from all batches (LOD, bulk/tapped density, sieve analysis [granule] and hardness, friability, disintegration, and compressibility characteristics [tablets]).

Once a satisfactory formulation from a physical characterization point-of-view has been arrived at, samples are submitted to the laboratory for chemical testing (dissolution profile, assay, content uniformity, etc.) as deemed appropriate.

It is recommended that dissolution-profile testing be undertaken on samples compressed at several hardnesses, so that the effect of varying the hardness on the dissolution profile can be established.

The development process is continued until one of the trial formulations demonstrates a close correlation to the Brandleader drug product as regards both physical and chemical results.

An example of such a formulation follows:

	Active/Excipients	mg/tablet	Comment
(i)	API	250.0	Required
(ii)	MCC	87.2	Diluent/compressibility enhancer/disintegrant/ dissolution aid
(iii)	Povidone	10.0	Binder (2.5%)
(iv)	Starch	20.0	Disintegrant (5%)
(v)	Citric acid	8.0	Stabilizer
(vi)	Starch (as paste)	20.0	Binder (5%)
(vii)	Stearic acid	4.0	Lubricant (1%)
(viii)	Magnesium stearate	0.8	Lubricant (0.2%)
(ix)	Purified water	q.s.	Granulation liquid

The Handbook of Pharmaceutical Excipients [45] should be consulted to confirm the quantities of the excipients selected.

This formulation is then scaled up in size to 10,000 to 20,000 units to provide sufficient samples for stability assessment. The physical/chemical testing is repeated to confirm that the larger batch provides comparable data with that yielded by the smaller trial.

Manufacturing Method

Items (i) to (iv), screened through an appropriate mesh (e.g., 20 mesh), are added to a suitably sized granulator/mixer bowl and mixed for 5 min under conditions of high-speed mix and shear. The citric acid (item (v)) is dissolved in a portion of purified water (ix) in a suitable stainless steel container. The starch (item (vi)) is added to form a slurry and then additional boiling purified water is added and vigorously stirred until a paste is formed. The paste is allowed to cool to ambient temperature and then added to the previously mixed powders and granulated for 5 min under controlled conditions using approximately 10% to 30% by weight of the granulating vehicle. The granules are dried in a fluidized bed drier [50°C–60°C] to a moisture level not exceeding 2% loss on drying. The dried granules are milled and transferred to a suitable tumble blender. Stearic acid (item (vii)) is screened through a 40 mesh and blended with the granule for 10 min before the addition of magnesium stearate (also prescreened through a 40 mesh) with final blending effected for 5 min.

Granules should be analyzed for LOD, bulk and tapped density, and sieve analysis. The resultant granules are compressed to a target weight of 400 mg.

Tablets should be compressed at three hardness ranges (low [2–8 kP], target [6–10 kP], and high [11–17 kP]) and friability, hardness, thickness, disintegration, and dissolution profiles determined.

It is important that tablets meet all physical and chemical acceptance criteria at both the lower and higher ends of the hardness range.

Results revealed that the target hardness generic formulation (Test 1) has a dissolution profile similar to Brand Lot 2, which is slower than Brand Lot 3 (faster-releasing Brand Lot) and faster than Brand Lot 1 (slowest-releasing Brand Lot) (Figure 4.6).

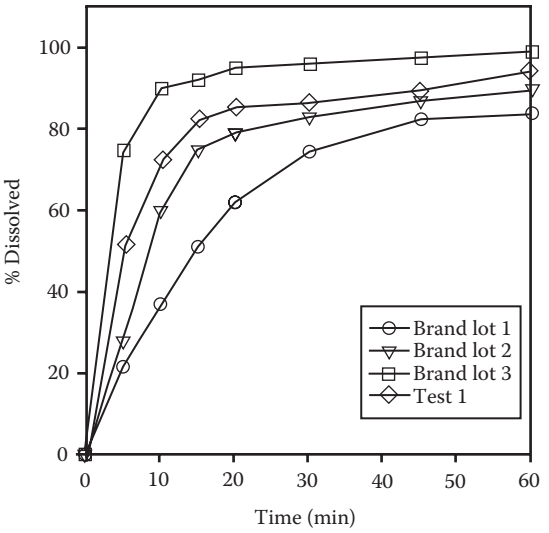


FIGURE 4.6 Comparative dissolution profiles of a generic product with a specific target hardness value versus three different brand lots of the same commercially available product.

Range Studies—Investigation of Formulation and Process Variables

Should the formulation prove stable under "accelerated" conditions of high temperature/humidity, "range studies" should be progressed to verify and assess the robustness of the formulation and process of manufacture.

The batch size should be the same as was employed for formulation development (2000–5000 units), and the campaign must contain a "control" batch, so that differences in excipient level and process of manufacture can be correctly interpreted.

Formulation Variables

Effect of binder level. Consider the effect of increasing/decreasing the binder level (e.g., by 1% of the total weight of this formulation). Provision for varying the binder level must be accommodated by reducing/increasing the amount of diluent to maintain a consistent tablet weight. Bulk and tapped density as well as sieve analysis of the final blend should be determined. In addition, granule flow and compressibility must be carefully monitored. Friability, disintegration, and dissolution rate testing must be performed in each case.

Figure 4.7 depicts the dissolution results that show that the effects of binder level variation by 1% were not significant.

However, nonuniform flow was observed in the tablets containing a lower binder concentration. This, together with the fact that the in vitro release rate did not decrease with increased binder concentration, demonstrates that an adequate amount of binder has been used.

Effect of disintegrant level. Similar experiments to those described above but increasing and decreasing instead, the level of disintegrant (starch) by a specified

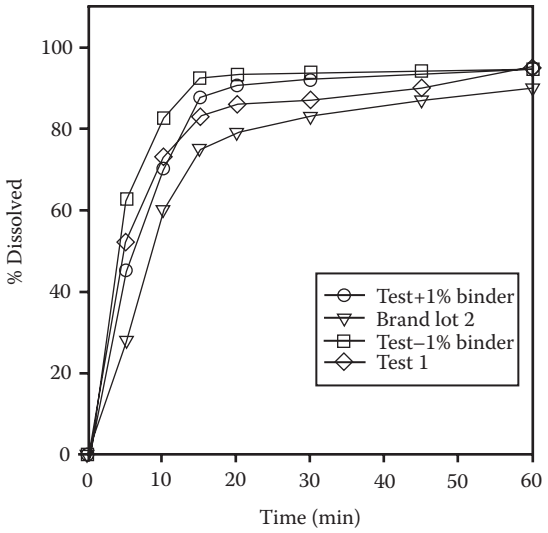


FIGURE 4.7 Comparative dissolution profiles showing the effects of binder concentrations.

amount (e.g., by 2%) is depicted. In both trials, compressibility was found satisfactory, whereas dissolution profiles (Figure 4.8) were comparable.

This demonstrates that a satisfactory level of disintegrant has been used.

It must be borne in mind that because microcrystalline cellulose itself possesses disintegrant properties, these may well override the effect(s) of starch.

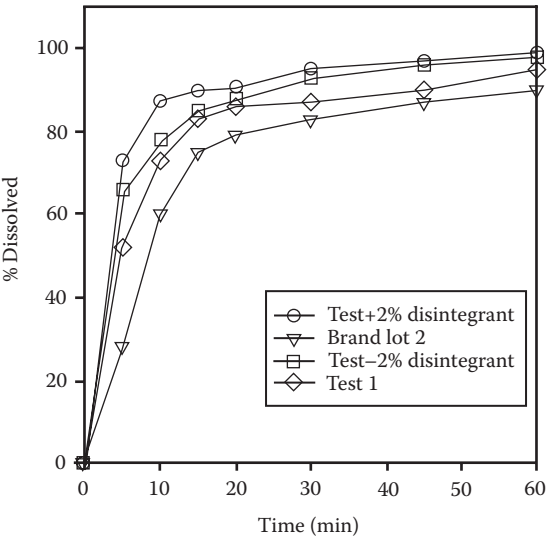


FIGURE 4.8 Comparative dissolution profiles showing the effects of disintegrant concentrations.

Effect of other formulation components. Further experiments describe the evaluation of a change in stabilizer concentration (increase/decrease by 0.5%), lubricant (increase stearic acid and magnesium stearate by 1.0% and 0.25%, respectively; decrease stearic acid and magnesium stearate by 0.5% and 0.1%, respectively), and granulation liquid (±10.0%).

Increasing or decreasing the level of stabilizer did not impact the dissolution profiles, but the full impact of change in stabilizer concentration requires assessment by comparing impurity profiles following accelerated stability testing. Changes in the lubricant levels affected the in vitro release profiles and the trial employing lower levels of both lubricants demonstrated sticking problems. The increase in magnesium stearate had a negative effect on tablet hardness and resulted in a slower dissolution rate.

Changes in the quantity of granulation vehicle had a slight effect on the dissolution profiles, but compression-related difficulties such as poor granule flow (due to under-granulation) were apparent.

In general, too little granulating vehicle can result in too fine a granule with associated poor flow, whereas too much granulating vehicle usually results in comparatively coarser granules providing tablets having a slower dissolution profile.

Dissolution profiles for each of these experiments are depicted in Figures 4.9 through 4.11.

Further increases in lubricant level from 1% to 2.5% of stearic acid and from 0.2% to 0.5% of magnesium stearate to reduce sticking were evaluated and the resultant dissolution profiles can be seen in Figure 4.12.

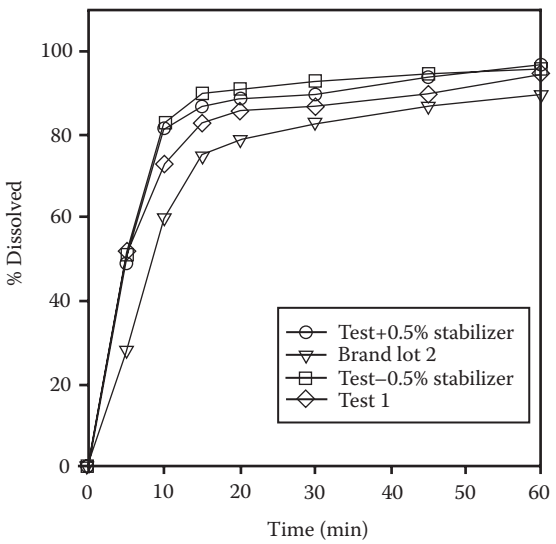


FIGURE 4.9 Comparative dissolution profiles showing the effects of stabilizer concentrations.

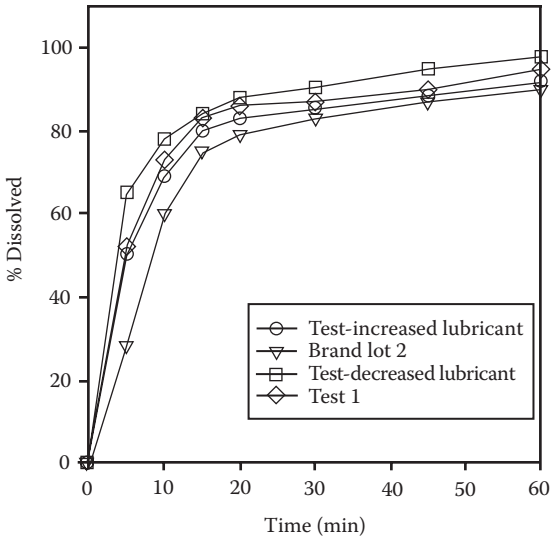


FIGURE 4.10 Comparative dissolution profiles showing the effects of increasing and decreasing lubricant concentrations.

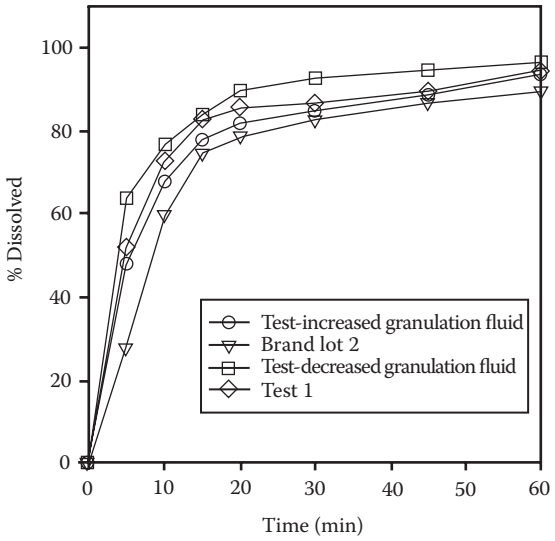


FIGURE 4.11 Comparative dissolution profiles showing the effects of increasing and decreasing granulation fluid.

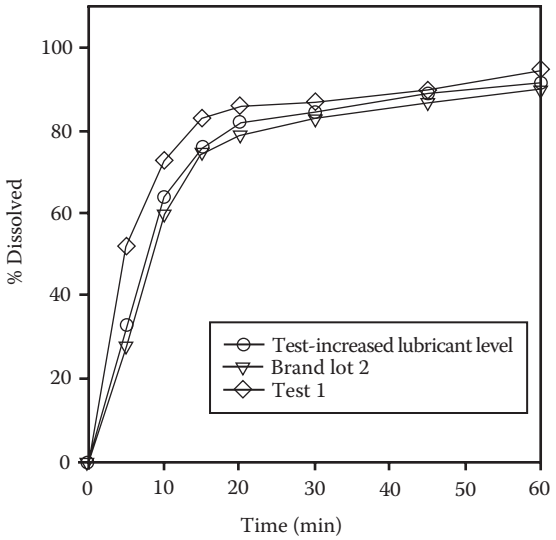


FIGURE 4.12 Comparative dissolution profiles showing the effect of increasing lubricant concentrations.

Process Variables

Typical variables that should be assessed include, among others, the granulation process (rate and quantity of granulation liquid addition, mixer and chopper conditions, over/under granulation, and the effects of over/under blending), dry-powder mixing time/speed, and the mesh size used for screening.

Samples from the resultant tablet batches should then be tested for compliance to specifications for hardness, disintegration, friability, and dissolution profile.

Effect of increasing lubricant mixing time. Doubling the mixing time should be evaluated to establish robustness. In this instance, no adverse effect on in vitro release profiles was seen (Figure 4.13).

Effect of increasing granulation time. Similarly, doubling the granulation time was evaluated for robustness and the in vitro release profile is depicted in Figure 4.14.

Once again, no marked changes to the dissolution profile were observed. In spite of satisfactory dissolution rates exhibited by the test formulations (Figures 4.13 and 4.14), the longer manufacturing times mitigate against using these process parameters for full-scale production.

Because the above series of trials challenging both the ranges of excipients and process variables provided results that confirmed that the formulation and process were sufficiently robust, and because data were available to demonstrate that the formulation was stable, exhibit-batch manufacture (comprising a minimum of 100,000 units or 10% of the envisaged commercial batch size, whichever is the greater) can now be embarked upon.

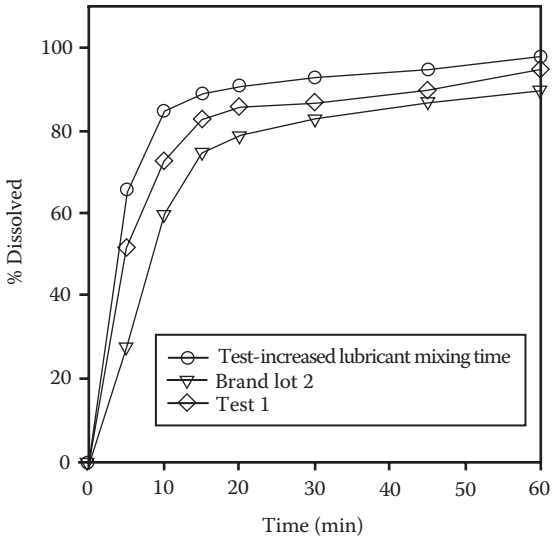


FIGURE 4.13 Comparative dissolution profiles showing the effect of increasing the lubricant mixing time.

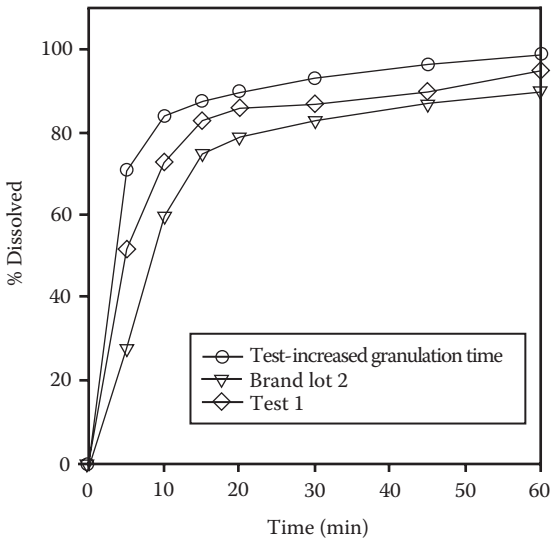


FIGURE 4.14 Comparative dissolution profiles showing the effect of increasing the granulation time.

Similarity and Difference Factors

As confirmation of acceptance of each formulation of the test product, difference (f_1) and similarity (f_2) factors [113] should be determined by performing the requisite dissolution rate testing on 12 units of each according to the FDA's Guidance on Dissolution Testing of Immediate Release Solid Oral Dosage Forms [114].

The difference factor (f_1) is a measurement of the relative error between the two curves, whereas the similarity factor is a measurement of the similarity in the percent dissolution between the two curves. If the f_1 values range between 0 and 15 and f_2 values range between 50 and 100, the dissolution curves being compared are considered similar or equivalent. The closer f_1 and f_2 are to 0 and 100, respectively, the better the comparability of the curves.

These factors can be determined using the following formulas:

$$f_1 = \left\{ \frac{\left[\sum \left| R_t - T_t \right| \right]}{\left| \sum R_t \right|} 100 \right\}$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{I}{n} \sum w_t (R_t - T_t)^2 \right]^{-0.5} 100 \right\}$$

where f = fit factor, R_t = reference assay at time t (percent dissolved), T_t = test assay at time t (percent dissolved), n = number of sample points, w_t = weighting at time t (optional), and $\sum$ = summation from $t = 1$ to $t = n$.

In the example above, it was noted that the dissolution profile depicted in Figure 4.12 for a formula with increased lubricant levels represented the formulation of choice. Calculated f_1 and f_2 values for this formulation relative to Brand Lots 1, 2, and 3 indicate that the test product is equivalent in vitro to only Brand Lot 2. The table below is a summary of all the calculated f_1 and f_2 values.

	Brand Lot 1 vs. Test[a]	Brand Lot 2 vs. Test[a]	Brand Lot 3 vs. Test[a]
f_1	39.8	4.6	14.4
f_2	30.5	72.8	42.2

[a] Test formulation—increased lubricant, depicted in Figure 4.12 (target hardness 6–10 kp).

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5 Scale-Up, Technology Transfer, and Process Performance Qualification

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INTRODUCTION

Generic product development aims at the formulation of a product bioequivalent and/or pharmaceutically equivalent to a specific reference listed drug (RLD). The regulatory authorities expect the product to have a robust, reproducible, and validateable manufacturing process consistently meeting critical finished product attributes throughout the product lifecycle. The formulation and manufacturing process developed by scientists, at a laboratory or pilot scale, must be scalable to large-scale production batches. Scale-up and technology transfer are crucial steps in pharmaceutical product development process. During this stage, Process Performance Qualification (PPQ) activities demonstrate the robustness and process capability of the manufacturing process and assure that the manufacturing process is capable of producing product that consistently meets predetermined quality attributes. Critical Materials, Critical Material Attributes (CMAs), Critical Process Steps (CPS), Critical Process Parameters (CPPs), Critical In-Process Controls, and Critical Quality Attributes (CQAs) are thoroughly examined during product development and the PPQ exercise. The process is scaled up to a batch size close to the biobatch or production batch after the initial development work. Design of Experiments (DOEs) and Quality Risk Management (QRM) principles should be employed to identify and understand critical parameters and their ranges and target settings. Depending on the complexity of manufacturing processes involved, such as dry blending, wet granulation, roller compaction, tableting, encapsulation, and coating, appropriate process parameters are carefully monitored and viable ranges are established. The process is evaluated at "bookend" of CPP ranges to set up appropriate controls for the manufacturing process.

The manufacturing process is transferred to production typically before product approval and launch. This may involve further scale-up of the batch size and other changes in the manufacturing process. These changes may be considered minor or major in a regulatory review and may require additional work, as per the "scale-up and post-approval changes" guidelines.

This chapter will focus on several issues related to these essential processes in generic drug development. All topics related to process characterization, equipment installation and operational testing, documentation, computer systems validation (CSV), and PPQ are discussed.

PRODUCT DEVELOPMENT

Scale-up, technology transfer, and PPQ are performed toward the terminal phase of the development cycle of generic products. However, the performance and success of these phases is affected by "upstream" activities such as formulation design and process characterization, in-process controls, finished product acceptance criteria, and test methodology. Because many of these are established at early stages of product development, it is imperative to address formulation and process development issues that can have pronounced effect on the manufacturing process, scale-up, and PPQ. Once a product is identified for generic development, various activities are initiated and a stepwise but parallel approach is taken in the development work, to include the following:

1. Preformulation studies
2. Formulation design and process development optimization
3. Scale-up characterization of manufacturing process
4. Process demonstration and technology transfer
5. PPQ
6. Documentation, registration, approval, and launch

Preformulation Studies

The manufacturing process utilized is affected by the variability in physical properties of the active pharmaceutical ingredient (API) and the excipients [1]. If the API component comprises the predominant portion of the dosage form, its physicochemical properties and variability, if not controlled, would influence mixing, granulation, flow, compression, and coating. Typically, the composition of the branded product is used as a guide in selecting excipients for the corresponding generic product. The formulation scientist needs to perform extensive work to identify the particular type or grade of excipient suitable for the product. The type of excipient can affect the manufacturing process and performance of the product and quality attributes of the finished dosage form. Excipient selection must be made, keeping in mind the final manufacturing process [2] intended for commercial production. This important consideration is often ignored in the early stages of product development, and often, improper selection of excipients and their inadequate characterization and control contribute to significant scale-up challenges during technology transfer and PPQ [3]. Table 5.1 provides a list of common excipients and their effect on manufacturing process and scale-up.

The formulation scientist must carefully review various physicochemical properties of the excipients and the resulting dosage form in selecting excipients and the manufacturing process. Excipients not only help in achieving target quality attributes, but proper excipient selection and control also influences the manufacturing process, ease of scale-up, and successful PPQ. In many instances, various excipient grades are available, differing in particle shape, size, degree of crystallinity, moisture content, flowability, and compressibility. Careful evaluation of the excipient properties in light of manufacturing process to be utilized is important. For example,

TABLE 5.1
Properties of Some Commonly Used Diluents for Tablets and Capsule Products

Component	Remarks
Dibasic calcium phosphate	Used in dry granulation (unmilled type) and wet granulation (milled type). Provides good hardness. High amounts in formulation may cause tablet hardness sensitive to compression force and may lead to lamination and capping.
Dibasic calcium phosphate dihydrate	Used in dry granulation (unmilled type) and wet granulation (milled type). Under certain conditions can lose the water of crystallization. Due to irreversible dihydration, accelerated stability of formula containing high amounts may lead to erroneous results.
Tribasic calcium phosphate	Used in dry granulation and wet granulation. Not a clearly defined chemical entity. High amounts in dry mix tablet formulation may cause capping and lamination.
Calcium sulfate	Used in dry granulation and wet granulation. Avoid anhydrous form that may convert into dihydrate during wet granulation or under accelerated stability conditions.
Microcrystalline cellulose, cellulose powder	Used in dry granulation and wet granulation. Improves tablet hardness if added dry. Improves granulation process and helps avoid batch failure due to overgranulation. High amounts in formulation increase tablet thickness and can render dry powder mixes more prone to overlubrication.
Dextrose anhydrous (granular), dextrose monohydrate	Used in direct compression, primarily in chewable tablets. Both the anhydrous and monohydrate forms are hygroscopic in nature and require handling at relatively low % relative humidity. Tablets are likely to harden on aging. Offers improved stability for drugs prone to oxidation. The anhydrous form may convert to monohydrate form on long-term exposure to high humidity.
Lactose monohydrate	Used in dry granulation and wet granulation. Select appropriate particle size grade. Fine-particle grade impalpable lactose improves mixing uniformity of potent micronized drugs. Excessive amount may cause compression problem.
Lactose anhydrous	Anhydrous form in wet granulation may convert into monohydrate and contribute to a 5.2% higher accountability. Spray-dried formulation is more susceptible to Maillard reaction and browning effect.
Maltodextrin	Various grades of particle size and bulk density exhibit difference in flow properties. Produces hard tablet. Formulations containing relatively high amount of maltodextrin should be processed at less than 50% relative humidity. Tablet hardness may increase with aging.
Mannitol	Used for chewable and regular tablets. It has high bulk density and good flow property. Not hygroscopic in nature. Produces hard tablets. Can be used in direct compression and wet granulation.
Starch	Used in dry mixing or wet granulation. A wide variety of grades vary in particle size, rate of hydration, compaction properties, etc. Facilitates mixing of potent drug and colors if used as a diluent. High amounts in formulation may result in poor compression and lubricant sensitivity. Avoid high amounts of lubricant.

lactose is available in several grades, including anhydrous direct tableting grade, a free-flowing spray-dried form (Fast-Flo), and several particle size grades of lactose monohydrate. While lactose monohydrate is useful both for dry mix and wet granulation, the anhydrous type should be avoided in aqueous granulation processes. The conversion of the anhydrous form to the monohydrate during aqueous granulation may contribute to approximately 5.3% weight gain, resulting in final batch yield discrepancies.

API and excipient material attributes and other considerations critical to the manufacturing process and scale-up of solid dosage forms are identified below:

1. Impact of excipient variability on product quality
2. Particle shape, size, and surface area (flow properties)
3. Solubility in water and granulating fluid
4. Crystallinity and polymorphism
5. Moisture sensitivity and equilibrium moisture content (EMC)
6. Bulk and tapped densities of major components
7. Granulation and drying properties
8. Compaction behavior
9. Potential changes during storage

Impact of Excipient Variability on Product Quality

Solid dosage formulations and processes are significantly impacted by material properties of the API and excipients. The sources of variation in product quality are attributable to complex interplay between CMAs of API and excipients and the manufacturing process as shown below:

$$\text{Product Variability} = f(\text{API Variability, Excipient Variability, Process Variability})$$

Usually, API properties and their impact on finished product quality are better understood compared with variability in excipients. There are several reasons for this, including naturally derived raw materials used as excipients, adaptation of food-grade materials for pharmaceutical uses, and their inherent lot-to-lot variability [4–6]. For example, many functional excipients used in the design of controlled release formulations are polymers. These polymers are rarely well characterized and controlled for their functional properties such as viscosity, particle size, and powder flowability. Even for excipients with existing pharmacopoeia monographs, the specifications listed are usually related to their chemical properties, whereas specifications corresponding to physical properties important for a formulation and process may not be identified. Recently, attempts are being made by the industry consortium—International Pharmaceutical Excipient Council, working with regulatory agencies, and the manufacturers and users, in addressing excipient variability and the role of performance testing, test methodology, and harmonization [7]. A draft United States Pharmacopeia Chapter <1059> Excipient Performance addresses this issue by identifying the CMAs of functionally categorized excipients and the performance tests that may be useful to characterize them [8]. There are numerous examples in the literature studying the effect of excipient variability on finished

product quality and the manufacturing process used to produce it [9,10]. Early formulation development and later scale-up trials should include such studies by intentionally selecting excipients covering normal variability in functional properties, for studying their impact on manufacturing and product CQAs. If such materials are not available from the excipient vendor, creative formulation approaches should be designed to incorporate this variability. For example, if a polymer matrix-based controlled release system is designed with a single specified viscosity grade, DOE studies may be performed with specific lots of polymer at the extremes of the viscosity range specified. If such lots are not available from the vendor, then DOE studies may be performed with mixtures of various viscosity grades to achieve the extremes of the specified viscosity range. A robust formulation and process design should be capable of handling typical lot-to-lot excipient variability. However, this should be studied upfront and critical material properties and their control strategy should be clearly identified.

Particle Shape, Size, and Surface Area

Particle shape and size and the size distribution of APIs and excipients can significantly affect their flow behavior. This is especially significant for products intended for manufacturing using direct compression technology. Spherical particles are ideal for dry mixing, whereas rod- and needle-shaped particles are difficult to process in dry mixing. Most pharmaceutical components (drug and excipients) fall between these two extremes. It is important to perform a thorough microscopic evaluation of the API and other major components of the formulation. The shape, size, surface morphology, and relative amounts of these components should be considered in selecting the manufacturing process. It is also possible to modify particle characteristics of materials for ease in the manufacturing process. For example, Povidone K90 is available as flakes and powder. The powder form is suitable for dry mixing, whereas flakes can be used as a binder that is dissolved in the granulating medium.

Solubility in Water and Granulating Fluid

If the manufacturing process utilizes the wet granulation method, the solubility of the drug and major excipients in the granulation fluid is critical. Water-soluble components will solubilize during a water-based granulation process and may form a dough-like mass that quickly results in overgranulation and makes drying difficult. If all components are water insoluble, the resulting granules will be soft due to poor binding, and the advantage of wet granulation to improve flowability and content uniformity may not be achieved. A powder mass containing a mixture of soluble and insoluble components in appropriate proportions provides excellent granules. For components that are susceptible to hydrolysis or require drying under milder temperatures, use of organic solvents such as ethanol or isopropanol may be the only alternative.

Crystallinity and Polymorphism

Many pharmaceutical materials exist in multiple polymorphic crystalline forms. Depending on the crystallization solvent and conditions, the drug substance may also form hydrates or solvates, usually referred to as pseudo-polymorphs. A careful

evaluation of the crystalline forms of API is important to avoid processing effects on crystal transformations and amorphous to crystalline transitions, which may have implications for finished product stability, dissolution behavior, and bioavailability. Before formulation development, it is important to establish the crystal properties of drug substances and critical excipients using x-ray powder diffraction and thermal analytical techniques. These techniques can also be used to monitor changes in crystallinity during processing and in the finished product on storage.

Moisture Sensitivity and EMC

Because water is typically used as the granulating medium, the binding property of moisture and equilibrium mositure content (EMC) of the formulation play a significant role in the granulation and drying processes. Hygroscopic materials such as polyethylene glycol, if present in large amounts in a formulation, are difficult to dry. In some instances, the hygroscopic nature of the drug may necessitate the use of special manufacturing facilities with strict humidity control. The EMC of major components generally dictates the final moisture content of the dried granules. The drying rate (drying curve) of a formulation can be theoretically estimated from the drying rate of the individual components. If the drug component is moisture sensitive, water should be avoided as the granulating medium. In such cases, ethanol or isopropanol may be used; however, the drying equipment (tray or fluid bed dryers) needs to be explosion proof because alcohols or other organic solvents have low flash points. Furthermore, the rate and extent of alcohol emission to the environment must be considered, because the Environmental Protection Agency has strict guidelines on alcohol emission that may vary from region to region.

Bulk and Tapped Densities of Major Components

The bulk and tapped densities of formulation components are easy to measure and provide valuable guidance for the flow property and in selection of the manufacturing equipment and processes. Low bulk and tapped densities indicate poor flowability of a material and require additional processing, such as roller compaction or wet granulation, to avoid production problems. Bulk densities of the major components affect the load size in the processing equipment (i.e., mixture and dryer) and govern the batch size. Equation 5.1 can be useful in estimating the batch size load from the bulk densities of the individual components:

$$B = 100 \times \{(a/D_a) + (b/D_b) + (c/D_c) + \ldots\}/V \tag{5.1}$$

where B is the percentage load in the mixer; V is the working volume of the mixer (liters); a, b, and c are the weights of the major components in the batch (kg); and D_a, D_b, and D_c are the bulk densities of the components a, b, and c (kg/L). If the calculated value of B is about 50% to 105%, the batch size can be considered appropriate depending on the type of equipment used.

Flow Parameters

The flow characteristics of individual components and the blend remarkably affect the manufacturing process. In addition to bulk and tapped densities, other flow

characterization measurements such as angle of repose, angle of spatula, floodability, and flow through a hopper should be evaluated for the blend. Typically, a material with high angles of repose, low floodability, and low bulk density contributes to manufacturing problems if not processed using wet granulation, slugging, or roller compaction.

Granulation Properties

The granulation properties of the drug and excipients are important for products manufactured using wet granulation. The ability of formulation components to hold the granulating fluid (kg fluid per kg material) can be measured alone or in combination. This information can be utilized in estimating the granulating fluid requirements for a scale-up using the following equation:

$$W = (A_1B_1 + A_2B_2 + A_3B_3 + \ldots) \times f, \tag{5.2}$$

where A_1, A_2, A_3, … are the weights (kg) of components 1, 2, 3, … in the batch; B_1, B_2, B_3, … are fluid holding capacities (kg fluid per kg material) of components 1, 2, 3, …; and f is a scale-up factor typically between 0.5 and 0.9. The amount of fluid required for the scale-up batch depends on other factors such as type of equipment, atomization, and rate of addition.

Drying Properties

The drying performance of a material is contingent on its ability to dry from a wet mass formed during the granulation process. Although various processing conditions such as drying temperature, relative humidity of the drying air, air velocity, and exposed granule surface area affect drying, the material affinity for the solvent dictates the drying rate. Small to medium molecular weight materials with low to medium water solubility lose water quickly and dry rapidly (e.g., lactose, calcium sulfate, and dicalcium phosphate). Some materials such as high molecular weight Povidone, hydroxypropylmethylcellulose, starch, hydrophilic gums, and polyethylene glycol are difficult to dry, especially if present in relatively high proportions in the formulation. However, an efficient drying technique such as use of the fluid bed dryer is useful to overcome drying problems for an otherwise difficult to dry material.

Compaction Behavior

The compaction behavior of tablet components plays a key role in the tableting process. The compaction property of the final blend is dictated by the individual components. Manufacturing processes such as wet granulation, roller compaction, and slugging can significantly alter compaction characteristics. In early preformulation, compaction behavior can be conveniently studied using an instrumented single station press (Carver or Korsch).

Potential Changes during Storage

Absorption and desorption of moisture and associated hardening and polymorphic conversion should be considered. Changes in physical characteristics of excipients

can have an adverse impact on manufacturing as well as quality characteristics of the finished product. The holding of the bulk quantity of the finished product before packaging may require special consideration for some products (e.g., orally disintegrating tablets and soft gel capsules). Appropriate hold studies should be conducted to demonstrate that holding the intermediates and in-process materials do not adversely impact downstream processing or product attributes. These studies should be conducted on drug, granulating and coating solutions, dry granulations, compressed tablets and capsules, and coated tablets before packaging. Some products may suffer physical damage if held in large quantities (drum or boxes) for several weeks under relatively high humidity or are transported in other facilities for packaging.

Formulation Design and Process Development Optimization

During early stages of product development, the qualitative and quantitative formulation composition is derived from laboratory-scale trials. The processing steps utilized to attain the desired performance characteristics of the dosage form are also identified. The work conducted during the formulation trial stage should reveal an understanding of the properties of active ingredient, excipients, and processing parameters that are critical to the intended quality attributes of the dosage form. At this stage, the development scientist should consider the design space to establish a range of process parameters and formulation attributes that consistently assure the quality of the product. The elements of QRM principles should be utilized when confirming the established ranges of formulation composition and processing parameters critical in achieving successful scale-up. This establishes an understanding of how the formulation and processing parameters influence product quality and performance in large-scale batches. A thorough understanding of the impact of manufacturing process on formulation components and the end product is achieved via implementing the Quality-by-Design (QbD) and DOEs as outlined below.

QbD in Generic Product Development

To improve efficiencies and modernize the pharmaceutical industry, in 2004, the US Food and Drug Administration (FDA) started a significant initiative titled "Pharmaceutical GMPs for the 21st Century: A Risk-Based Approach" [11]. An important part of this initiative was to shift the industry focus away from Quality-by-Testing to QbD, whereby drug development ensures enhanced understanding of the product and process. The International Conference on Harmonization (ICH) guidelines—ICH Q8: Pharmaceutical Development [12], ICH Q9: QRM [13], and ICH Q10: Pharmaceutical Quality Systems [14]—provide the abstract-level background on how QbD impacts and ensures drug product quality. The FDA's Office of Generic Drugs (OGD) has published several reports and presented at public industry forums, focusing and defining QbD specifically for generic product developers [15–17]. In addition, in 2007, the OGD implemented the question-based review for the CMC section of the Abbreviated New Drug Applications (ANDAs) [18]. This new process implemented several elements of QbD into the review process, including

incorporation of Quality Overall Summary, where the ANDA sponsor is expected to address all question-based review questions. More recently, the OGD has issued specific product development examples for immediate-release and modified-release dosage forms, incorporating in-depth elements of QbD [19,20] and QRM. Lionberger et al. [17] have briefly summarized the QbD-based development process for generics to include the following steps:

1. Identify a Quality Target Product Profile (QTPP). QTPP can be defined as the quantitative surrogate for aspects of clinical safety and efficacy that can be used to design and optimize the product and manufacturing process. For generic products, the QTPP is derived from the RLD label. QTPP for more complex products may include several additional targets in addition to the basic elements such as biphasic in vitro drug release to capture immediate-release and modified-release portions of a dosage form, partial area under the curve in vivo requirements to capture relevant pharmacokinetic/pharmacodynamic requirements of the RLD, and avoidance of alcohol-induced dose dumping for extended-release products [16].
2. Compile relevant prior knowledge about drug substance, potential excipients, and process. Use risk assessment tools to identify gaps for further development.
3. Identify CQAs of the product being developed. CQAs can be defined as physical, chemical, biological, or microbiological properties that need to be controlled to ensure drug product quality. CQAs are usually derived from the QTPP and for solid dosage forms may include (but not limited to) identity, assay, purity/impurity, stability, and dissolution.
4. Design a formulation and identify Critical Materials and CMAs of the drug substance, excipient, and in-process materials. CMAs may include drug substance or excipient particle size, specific surface area, bulk/tapped density, viscosity, impurity levels, etc.
5. Design a manufacturing process and identify CPPs. A process parameter can be considered to be critical when a realistic change in that parameter may cause the product to fail to meet the CQAs.
6. Using risk assessment tools to identify CMAs and CPPs that require control (see below Control Strategy) to achieve CQAs of the finished product. Additionally, DOEs may be used to gain better understanding of the interplay between CMAs, CPPs, and CQAs. A further brief description on the use of DOE in pharmaceutical development is given below.
7. Establish a control strategy for the entire manufacturing process. This may include controls on incoming raw materials, in-process controls, proven acceptable ranges around specific parameters of a unit operation, and finished product tests and specifications. The strategy should include expected changes on scale-up, guided by further risk assessment performed at the larger scale.
8. Monitoring the manufacturing process throughout the product lifecycle to produce a product with consistent quality and also to implement continuous improvement.

As described above, QbD plays a key role not only in early product development, but also significantly influences scale-up of the manufacturing process, to the pilot scale and at later stages to the commercial scale. For generic products, use of DOE to gain a better understanding of the product and process is established at the small scale and verified at the commercial scale [21]. For this approach to be successful, a clear identification of scale-dependent and scale-independent process variables along with evidence of prior knowledge with similar unit operations should be demonstrated by the ANDA sponsor [22].

Design of Experiments (DOEs)

In the new QbD paradigm, significant emphasis is placed on the use of DOEs to gain a better understanding of the product attributes and process parameters and how they impact the finished product CQAs. Development of a pharmaceutical product is essentially a technique wherein the physicochemical properties of the active ingredient, excipients, and the manufacturing process are manipulated to achieve desired quality in the finished dosage form. The traditional method of varying "One-Factor-at-a-Time" approach is less dependable and more time consuming and often provides an apparently (or marginally) acceptable formulation and process rather than characterizing the desired ranges and multivariate interactions of interest. In today's competitive market, statistically designed experiments in product and process development are becoming increasingly necessary because they are quick and cost-effective. Analysis of data from statistically designed multivariate experiments enables one to generate a mathematical model and contour plots that elucidate formulation and process parameters affecting the product quality attributes. Various software packages [23–25] are available for designing experiments, developing mathematical model, and generating response surfaces. However, the success of statistical design depends on the careful selection of factors, the use of meaningful ranges of these factors, and a specific experimental design to be utilized in the study. Optimization requires statistical skill in addition to an understanding of the CMAs of drug substance and excipients involved and their impact on the process. Identification of CMAs and CPPs from risk assessment tools and an understanding of the expected relationship between them and their impact on CQAs are crucial to the success of this approach. A brief description of experimental designs applicable in product and process characterization is given here. A sample of CPPs and the CQAs impacted in a typical tableting operation is summarized in Table 5.2. For understanding the effect of multiple process variables on product quality, factorial designs are widely chosen. The independent variables in experimental design must be carefully selected, because increasing the number of variables results in a large increase in the potential number of experiments. However, the number of experiments can be minimized by carefully modifying the design and levels of factors to be studied. Accordingly, one may choose to use full factorial, fractional factorial, orthogonal composite, nonorthogonal symmetrical composite, central composite, or noncentral composite design. The composite design is made by adding extra points (star points) to the two-level factorial or fractional factorial design. If n is the number of factors to be studied, the additional points required for the composite design is $2n + 1$, one at the center

TABLE 5.2
Typical Unit Operations, Process Parameters, and Potentially Impacted Quality Attributes

Pharmaceutical Unit Operation	Process Parameter	Quality Attributes
Mixing	Type and geometry of mixer	Blend uniformity
	Order of addition	Particle size distribution
	Mixer load level	Bulk/tapped density
	Number of rotations	Moisture content
	Agitator bar (ON/OFF)	Flow properties
Milling	Impact/Cutting/Screening Mills	
	Mill type	Particle size distribution
	Speed	Particle shape
	Blade configuration/type	Bulk/tapped density
	Screen type and size	Flow properties
	Feed rate	Polymorphic form
	Fluid Energy Mill	
	Number of grinding nozzles	
	Feed rate	
	Nozzle pressure	
	Classifier type	
Wet granulation	High Shear Granulation	
	Pre-binder mixing time	Power consumption (kW)
	Impeller speed/configuration/location	Blend uniformity
	Chopper speed/configuration	Flow property
	Spray nozzle type/location	Particle size and distribution
	Method of binder addition	Granule size and distribution
	Binder fluid temperature	Solid form
	Binder addition rate/time	
	Post-granulation mix/kneading time	
	Bowl/product temperature	
	Fluid Bed Granulation	
	Mixing time	
	Spray nozzle type/number/pattern/configuration	
	Method of binder addition	
	Binder fluid temperature	
	Binder fluid addition rate/time	
	Inlet airflow, temperature, volume and dew point	
	Exhaust air temperature and flow rate	
	Filter property and size	
	Filter shaking intervals	
	Product temperature	

(*continued*)

TABLE 5.2 (Continued)
Typical Unit Operations, Process Parameters, and Potentially Impacted Quality Attributes

Pharmaceutical Unit Operation	Process Parameter	Quality Attributes
Drying	Fluid Bed Dryer	
	Inlet air volume, temperature, and dew point	Granule size and distribution
	Exhaust air temperature and flow	Granule strength and uniformity
	Filter properties	Particle size
	Filter shaking intervals	Flow
	Product temperature	Bulk/tapped density
	Total drying time	Moisture content
		Residual solvents
	Tray Dryer	
	Number of carts and trays per chamber	
	Amount of product per tray	
	Drying time and temperature	
	Airflow	
	Inlet air dew point	
	Vacuum/microwave dryer	
	Jacket temperature	
	Condenser temperature	
	Impeller speed	
	Vacuum strength	
	Microwave frequency	
	Electric field	
	Energy supplied	
	Product temperature	
Roller compaction	Roll speed	Appearance
	Gap setting	Ribbon/particle size and shape
	Roll pressure	Ribbon density, strength, and thickness
	Auger screw rate	Solid form
	Roller type	
Compression	Compression speed and force	Target tablet weight
	Precompression force	Weight uniformity
	Feed frame type and speed	Content uniformity
	Hopper design, height, and vibration	Hardness
	Tablet weight and thickness	Thickness
	Depth of fill	Tablet porosity
	Punch penetration depth	Friability
		Visual attributes
		Moisture content

(*continued*)

TABLE 5.2 (Continued)
Typical Unit Operations, Process Parameters, and Potentially Impacted Quality Attributes

Pharmaceutical Unit Operation	Process Parameter	Quality Attributes
Coating (fluid bed and pan)	Product temperature	Weight of core tablets
	Total pre-heating time	Appearance
	Spray nozzle type/number/pattern/configuration	Visual attributes
	Individual gun spray rate	% Weight gain
	Total spray rate	Film thickness
	Pan rotation speed	Color uniformity
	Atomization air pressure	Hardness
	Pattern air pressure	Thickness
	Inlet airflow, temperature, and dew point	Friability
	Exhaust air temperature and airflow	
	Product temperature	
	Total coating time	

Source: Adapted from Yu, LX. Pharmaceutical quality by design: Product and process development understanding and control. *Pharm Res* 2008 April; 25.

and the remaining $2n$ in pairs along the coordinate axis. An example of a central composite design is given in Table 5.3. In this orthogonal composite design, the value of 1.215 (axial point) at the six composite points (Experiments 9–14) depends on design specifics such as number of factors and experiments. Table 5.4 shows the total number of experiments and the values of axial points for several designs. It also shows the benefit of a composite design over a three-level factorial design. The increase in the number of experiments due to an increase in the number of factors is significantly higher in the case of a three-level factorial design compared with a fractional composite design.

Details of experimental design are available in various publications [26–29]. It is recommended that some initial screening trials be performed to gain an understanding of the effect of each variable and the ranges of parameters to be evaluated in a DOE. This adds tremendous value in developing a design with a minimal number of experiments yet capturing the target formulation and processing conditions.

Scale-Up Characterization of Manufacturing Process

High-speed production of large-scale batches using modern technology has become essential in minimizing manufacturing costs to improve the profit margin in today's competitive market. Increases in batch size or scale-up are accomplished by using larger, high-speed equipment that may require adjustments to the process parameters

TABLE 5.3
Example of Central Composite Design Used in Product Development DOE

	Factors (Independent Variables)			
Experiment	**Factor A**	**Factor B**	**Factor C**	***n* = 3**
1	+1	+1	+1	Factorial design (2^n)
2	+1	+1	–1	
3	+1	–1	+1	
4	+1	–1	–1	
5	–1	+1	+1	
6	–1	+1	–1	
7	–1	–1	+1	
8	–1	–1	–1	
9	+1.215	0	0	Composite points (2^n)
10	–1.215	0	0	
11	0	+1.215	0	
12	0	–1.215	0	
13	0	0	+1.215	
14	0	0	–1.215	
15	0	0	0	Center point

TABLE 5.4
Number of Experiments and Axial Points for Several Designs

Variables	**Three-Level Factorial**	**Composite Design**	
n	**3^n**	**$2^n + (2^n + 1)$**	**Axial Point**
2	9 (full factorial)	9 (full factorial)	1.000
3	27 (full factorial)	15 (full factorial)	1.215
4	81 (full factorial)	25 (full factorial)	1.414
5	243 (full factorial)	43 (full factorial)	1.596
5	81 (1/3 fractional)	27 (1/2 fractional)	2.041
6	729 (full factorial)	77 (full factorial)	1.761
6	243 (1/3 fractional)	45 (1/2 fractional)	1.724

established using small-scale equipment. However, the in-process and finished products must meet all predetermined specifications, and the products from scaled-up and pre-scaled-up batches must be physically, chemically, and biopharmaceutically equivalent. The first and foremost step in scaling up is the establishment of batch size requirements. Batch sizes in generic industries are often determined arbitrarily and may require further scale-up or scale-down depending on available equipment sizes and predicted market demand. It is important to identify an optimal batch size

rather than the maximum size possible. Several factors that need to be considered in determining batch sizes are the following:

1. Market demand predictions
2. Available production capacity
3. Cost of the batch
4. Stability of the finished product
5. Analytical testing efficiency

The manufacturing process and operating parameters utilized in smaller batch manufacturing are to be considered in the scale-up plan. The technology and equipment used in the development process often impose several constraints during scale-up work. Because pharmaceutical products are usually manufactured using several discrete batch processes, it would be appropriate to discuss the scale-up of each of these unit operation processes. The following are some of the most common pharmaceutical unit processes used in the manufacture of solid dosage forms:

1. Dry blending
2. Wet granulation
3. Roller compaction
4. Milling
5. Drying
6. Extrusion/spheronization
7. Compression
8. Encapsulation
9. Coating
10. Fluid-bed processing

Dry Blending

Dry blending is often the most common unit operation in the pharmaceutical industry due to its simplicity and use of less complicated equipment. However, several factors are to be considered while scaling up a dry blending process [30]. Equipment considerations such as blender type and design, blender load, mixing speed, use of auxiliary dispersion equipment such as intensifier bars and choppers, and the dynamics of mixing action produced within the mixer need careful evaluation. Formulation variables that influence a mixing operation are particle shape and size distribution and cohesiveness of major components, their bulk densities, and the order of addition of various components into the blend. Mixer selection should be based on the assessment of cohesive nature and the flowability of the ingredients to be mixed. Low shear tumble blenders, such as bin blenders (Bohle, TOTE Blenders), V-blender (Patterson–Kelley) and double cone blender (Gemco), are well suited for mixing free-flowing and slightly cohesive powders. V-blenders are widely used in handling potent drugs due to their ability to mix by geometric dilution and ease for containment. However, improper load (too high or too low), and wide difference in ingredient particle size and shape, may lead to segregation. Intermediate shear

mixers such as the orbiting screw mixer (Nauta), ribbon blender, and shaking mixer (Turbula) are used for blending free-flowing powders that are moderately cohesive. High shear mixers (Diosna, Collette–Gral) are recommended for powders that are highly cohesive and not free-flowing to break lumps and improve mixing. The drug components are often sandwiched between other excipients to improve dispersion and prevent loss of drug (especially low dose) due to their preferential adherence to the interior surface of the mixer. If the drug ingredient is highly cohesive, it may be beneficial to screen the premix before final blending. To avoid segregation of free-flowing powders, particle size reduction of one or more components of the blend before mixing may be essential. This can be achieved by including a milling step in the compounding process. Geometric dilution is often employed to aid uniform mixing of low-dose actives. In scaling up tumble blenders of similar design, rotational speed may be reduced relative to the smaller mixer to achieve dynamic similarity (i.e., similar Reynolds number). However, mixing times may be increased to provide a constant number of rotations [31]. In some instances, increased mixing times may have an adverse effect on the manufacturability of the product (e.g., tablet capping due to overlubrication or increased segregation potential due to overmixing). Several manufacturers of tumble blenders provide scale-up factors for determining the mixing times in large mixers from experiments performed in small mixers. Table 5.5 summarizes the working capacities, blender load levels, and scale-up factors for twin-shell blenders without the agitator bar. These factors are useful in calculating mixing times during blending scale-up operations.

Usually, such factors are not applicable when dry blending in high shear mixers. These are very efficient in mixing cohesive powders by increasing shear forces and thus improving deagglomeration efficiency. Mixing times are usually kept constant when scaling up in such mixers, providing constant impeller tip speeds. However, segregation potential may increase in high shear blending, especially when components with large differences in particle shapes and sizes exist within the blend. Blend uniformity is usually recognized by following a well-established sampling

TABLE 5.5
Scale-Up Factors for Selected Twin-Shell Blenders

Working Capacity (ft^3)	Total Capacity (ft^3)	Shell Diameter (in.)	Scale-Up Factor[a]
1	1.68	11.5	1.3
3	5.16	16.5	1.6
5	8.42	19.5	1.7
20	33.83	31.0	2.0
50	82.95	42.0	2.2
100	174.95	54.0	2.8

Source: Patterson–Kelley Company (East Stroudsburg, PA).

[a] Blending time in large blender = [(Scale-up factor for larger blender)/(Scale-up factor small blender)] × (Blending time in small blender).

plan based on the mixer type and geometry. The drug content assay of the sampled blend must meet preestablished criteria.

Wet Granulation

The wet granulation process offers several advantages over dry blending. Wet granulation provides effective distribution of low-dose actives, increased densification of low bulk density materials, and improved flowability and compressibility of the final blend. Although several wet processes are feasible, granulation employing low/high shear mixers and a fluid bed are more often used in the pharmaceutical industry and will be discussed here.

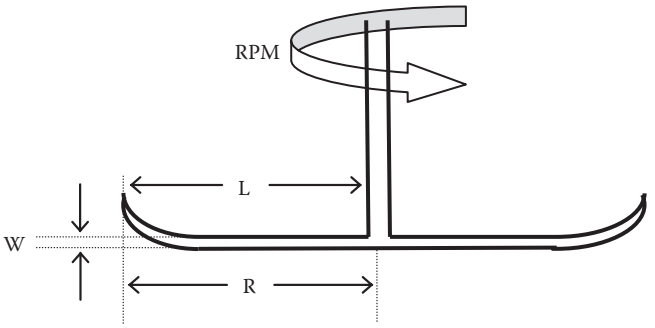
Low shear granulation employs mechanical agitation at slow speed, such as in ribbon and paddle mixers, planetary mixers, orbiting screw mixers, and sigma blade mixers, or rotating granulators such as twin-shell blenders with an intensifier bar/spray head combination. These granulators usually produce fluffier granules with lower bulk density compared with high shear granulation, which may be the desired property for some products. Important factors to consider during scaling up in rotating blenders include liquid addition rate, spray droplet size, intensifier bar/spray head design, and shell and intensifier bar rotation speeds.

Successful scale-up in mechanically agitated low shear mixers depends on the ability to monitor the granulation process during liquid/binder addition and subsequent wet massing. Researchers have suggested several techniques, such as infrared moisture sensors, torque measurement, current monitoring, and power consumption, to detect granulation endpoint. Luenberger [32] identified five distinct phases during wet granulation in a planetary mixer using a power consumption meter and stated that useful granules could be produced during the third phase. Landin et al. [33] and Faure et al. [34] used the concept of relating power consumption to several process and formulation variables in scaling up granulations in planetary mixers. The variables evaluated were impeller rotation speed and dimensions, wet mass density and consistency (measured using a mixer torque rheometer), and fill ratio (height of wet mass/bowl diameter). Using data obtained for mixers of different sizes, they came up with a relationship between the power number (Np) and Reynolds number (Re), Froude number (Fr), and the bowl fill ratio, that is, $Np = f(Re, Fr, \text{fill ratio})$. The Reynolds number represents the ratio of dynamic to viscous forces, whereas the Froude number represents the ratio of dynamic force in the mixer to the gravitational force. This relationship is useful in predicting consistent granulation endpoints during scale-up [33,34].

Wet granulation in high shear mixer granulators is the method of choice due to shorter process time, superior granule properties, and process reproducibility. High shear granulation offers several advantages, including densification of low bulk density materials, lower binder requirement, control over porosity of granules, and easy cleaning. Several designs of bowls, impellers, and choppers are available from different manufacturers. The most common design has the impeller shaft rotating in the vertical plane. The impeller could be bottom driven inside a fixed bowl, such as in Diosna, PMA/Fielder, and VG/Powrex (Glatt) mixers. In a variation of this design, the impeller and chopper are top driven inside a detachable bowl, such as in Collette-Gral, GMX/Vector, Huttlin, and Bohle mixers. Several of these granulators are

available as single-bowl systems, where the product can be granulated and vacuum/microwave dried inside the same bowl. Some of these mixer-granulators have been thoroughly characterized with respect to their processing parameters [35–37].

Several reports concerning scale-up in high shear granulators have been published [38–43]. Some important parameters and terminology used in the scale-up of high shear granulation are depicted in Figure 5.1. Table 5.6 lists critical scaling-up parameters for Collette-Gral high shear mixer/granulators. Rekhi et al. [44] studied the effect of scale-up in three geometrically similar Fielder high shear mixers. They concluded that three factors govern successful scale-up: (a) impeller speed adjustment to keep the tip speed constant, (b) linearly scaled-up amount of granulating fluid based on batch size, and (c) granulation time adjustment based on ratio of impeller speeds in different sized mixers [44]. In one study, normalized impeller work was used for predictable endpoint control in high shear granulation containing high amounts of microcrystalline cellulose [42]. Horsthuis et al. [40] studied lactose formulations in 10-, 75-, and 300-L Gral mixers and obtained different power curves for each of these mixers, because Gral mixers are not geometrically similar. However, they found good correlation between granulation endpoint and the Froude number (Fr) but not a predictable relation with tip speed or relative swept volume. Landin et al. [43] and Faure et al. [39] used relationships between dimensionless



Angular velocity, $\omega = 2\pi/60 \times RPM$
Tip speed, $V_T = \omega \times R$
Projected impeller blade area $A_b = N \times w \times L$
Swept volume $= \omega \times R \times A_b$
Relative swept volume $(s - 1) = W/(p\omega RA_b)$
Bowl fill ratio $= \rho R_b{}^3/W$
Power number, $N_p = \Delta P/(\rho\omega^3 R^5)$
Reynold's number, $Re = \rho\omega R^2/\mu$
Froude number, $Fr = R\omega^2/g$

Where:
R is the impeller radius
N is the number of blades on impeller
L is the effective length of blade
w is the width of the blade
W is the amount of wet mass
ρ is wet mass bulk density
R_b is the bowl radius
ΔP is the net power consumption of the mixer
μ the wet mass consistency (measured using torque rheometer)
g is the gravitational constant

FIGURE 5.1 Description of several scale-up terms and concepts used in wet granulation.

TABLE 5.6
Upscaling Gral High Shear Mixer-Granulators

Gral (liters)	10	25	75	150	300	400	600	1200
Bowl content (liters)	7.9	27.0	77.0	153.0	303.0	400.3	614.0	1166.0
Height (cm)	18.0	26.0	38.0	45.0	60.0	60.0	70.0	70.0
Width (cm)	24.6	37.5	52.5	69.2	84.2	96.2	109.2	149.2
Radius of mixing arm (cm)	11.9	18.0	25.4	33.5	40.0	46.0	52.5	72.50
Width of mixing blade (cm)	2.5	3.5	5.5	7.0	6.0	6.4	8.0	11.0
Thickness of mixing blade (mm)	6.0	8.0	12.0	15.0	15.0	20.0	20.0	25.0
Surface of mixing blade (cm^2)	23.8	48.0	110.0	198.0	197.0	242.0	348.0	610.0
Angle of inclination of mixing blade	55.0	55.0	55.0	55.0	55.0	55.0	55.0	155.0
Speed 1 (rpm)	430	283	206	145	120	103	95	79
Speed 2 (rpm)	650	423	300	218	185	155	135	119
Tip speed @ speed 1 (m/s)	5.36	5.33	5.48	5.09	5.03	4.96	5.22	6.00
Tip speed @ speed 2 (m/s)	8.10	7.97	7.98	7.65	7.75	7.47	7.42	9.03
Froude number @ speed 1	2243	1470	1099	718	587	497	483	461
Froude number @ speed 2	5125	3283	2330	1623	1396	1127	975	1047
Swept volume (dm^3)	0.764	2.356	7.536	18.234	20.998	30.129	45.635	130.842
Relative swept volume @ speed 1 (s^{-1})	0.6931	0.4116	0.3360	0.2880	0.1386	0.1292	0.1177	0.1477
Relative swept volume @ speed 2 (s^{-1})	1.0477	0.6152	0.4894	0.4330	0.2137	0.1944	0.1672	0.2226

Source: Courtesy of Collette-Gral Division, GEA Pharma Systems.

numbers (power, Reynolds and Froude numbers) and bowl fill ratio for scaling up in fixed bowl (Fielder) and removable bowl (Gral) mixers, respectively, with some success. In spite of such reports on scale-up in high shear mixers, this topic is not well developed [38].

Fluid bed is the other commonly used approach for wet granulation and concurrent drying. Some important factors to consider during scaling up in a fluid bed

granulation are fluidization velocity of process air, ratio of granulation spray rate to drying capacity of fluidization air, inlet air temperature, bed depth, and droplet size of the sprayed binder [45,46]. It is recommended that one use the same inlet temperature, droplet size, and air velocity (airflow/area of screen size) and achieve the same fluidization level when transferring the process from smaller equipment to production scale. The spray rate for the larger unit may be calculated using the following equation [47]:

$$R = (B/b)r, \tag{5.3}$$

where R is the spray rate in the larger unit (g/min), B is the bowl screen area for the larger unit (ft^2), b is the bowl screen area for the smaller unit (ft^2), and r is the spray rate in the smaller unit (g/min). Small adjustments may need to be made to such theoretical calculations to account for differences in bed depth [47].

Roller Compaction

Roller compaction involves continuous compaction of drug–excipient blends into ribbon-like compacted material, which is subsequently milled, lubricated, and either compressed into tablets or encapsulated. Roller compaction, as a pharmaceutical unit process, has several advantages over other particle enlargement techniques such as wet granulation. For high-dose, water-soluble drugs, aqueous granulation is not the preferred method due to inadequate water distribution and formation of lumps. For drugs that are chemically unstable in the presence of water or the granulating solvent, roller compaction offers an effective alternative for granulation. Several equipment and process parameters have to be addressed when scaling up a roller compaction granulation [48]:

1. Roll configuration or design: smooth, corrugated, or concave-convex
2. Roll diameter, nip angle, and area
3. Screw feed rate
4. Roll speed
5. Compaction pressure
6. Feed screw orientation vertical or horizontal
7. Vacuum deaeration of the blend before compaction

Nip angle is the angle made by the powder being compacted by the rolls in the compaction (nip) region [49]. Highly compressible materials have large nip angles compared with incompressible materials. Corrugated rolls have a higher capacity to drag material between the rolls compared with smooth rolls and hence provide greater compaction forces. It is important to maintain these design similarities between compactors when scaling up from a laboratory or pilot unit to the production equipment. Sheskey et al. [50] studied the effect of several process parameters during scale-up of a hydroxypropylmethylcellulose containing controlled release matrix formulation of theophylline. They scaled up the roll speed by maintaining the same linear velocity as that obtained from the laboratory unit, thus providing similar dwell time for the material in the compaction zone. Keeping the parameter

force/linear inch constant, the compaction force was scaled up to the production unit. Finally, the screw speed to roll speed ratio was kept constant for all units. Using these scale-up factors, reproducibly consistent granules and finished tablets were produced in the laboratory-, pilot-, and production-scale equipment. However, dissolution similarity (f_2 factor) was only established for the laboratory- and pilot-scale formulations but not the production-scale one. Based on the predicted in vivo performance of these formulations, the authors concluded that the production-scale equipment produced a faster releasing formulation compared with smaller units [50]. For successful scale-up, it is important to evaluate compaction rate (kg/min) and applied pressure as well as milling parameters, that is, milling rate (kg/min/screen surface area) and mill speed. The particle size distribution of the processed material provides valuable information about the reproducibility of the process.

Drying

Drying is a commonly employed unit process in the manufacture of solid dosage forms. Drying in the pharmaceutical industry is accomplished using static bed dryers (tray or truck ovens), moving bed dryers (turbo-tray dryers), fluidized bed dryers, and spray dryers. More recently, single-pot systems incorporating high shear mixer-granulators with vacuum, microwave, or infrared drying are also becoming popular [51]. Depending on the desired final product characteristics, any of these dryers may be employed. The commonly used dryers in solid dosage form manufacture (i.e., tray dryers and fluid bed dryers) are discussed here. Critical factors governing the drying process include the EMC of the formulation blend, the exposed surface for solvent transfer, and the vapor carrying capacity of the drying air. Psychometric principles for calculating the vapor carrying capacity of air should be employed in scaling up a drying process. Some important factors while scaling up a tray-drying process are the number of trays, product load per tray (bed thickness), temperature, and humidity of the circulating air inside the oven. Maintaining the same bed thickness (kg/tray) and providing similar drying air capacity will facilitate successful scale-up from pilot-scale to production-scale dryers.

Fluid bed drying processes are more challenging to scale-up [52,53]. Several factors impacting the drying process include airflow, air temperature, bed depth, and product characteristics. The fluidization air volume should be adjusted to keep the same air velocity (ft/min) between different sized units. Inlet temperature, dew point, and the product bed temperature in the scaled-up larger batch should be maintained as in the smaller unit. However, some adjustments to these parameters may be made depending on relative differences in fluidized bed heights between different units.

Milling

Milling is commonly employed to reduce particle size of granulations, bulk drug substances, and excipients to facilitate uniformity of powder mixes. This process is also used to manipulate the dissolution profile of the dosage form. Following wet granulation, wet milling is often employed to improve the granule surface area for more efficient drying. Sizing of granulation is typically accomplished using either low-energy mills (oscillating granulators) or high-energy mills (hammer, conical, and centrifugal impact mills). The hammer mill is the most common and versatile

machine used in the manufacture of solid dosage forms. It consists of either a swinging or fixed rotor, which forces the material against a fixed screen. Various factors such as rotor shaft configuration (vertical/horizontal, fixed/swinging), granulation feed rate, blade type (hammer or knives), rotor speed, and screen size and type (mounting, screen thickness, rasping, or regular screens) are to be considered while scaling up a hammer mill process. The particle size of the milled material is smaller than the corresponding screen size because particles enter the screen holes tangentially [54]. This effect is more pronounced at higher rotor speeds. Narrow particle size distributions are obtained at medium and high speeds compared with low speed. Several scale-up factors for Fitzpatrick hammer mills are summarized in Table 5.7.

A conical mill (Comill) consists of a conical screen inside a milling chamber along with a rotating impeller. Comills use less energy than hammer mills and are well suited for milling heat sensitive and difficult to mill materials. The impeller configuration (knife, round, or sawtooth edges), impeller speed, and screen size affect the properties of the milled product in a Comill.

Extrusion/Spheronization

This technique is primarily used to produce approximately spherical granules in a narrow particle size range for controlled release products. The major advantage of this process is its ability to incorporate high drug loads in the granulation. The dry mixing, wet granulation, and drying aspects of this technique are similar to those of most pharmaceutical wet granulations.

During the extrusion process, a wet mass (granulation) is forced through dies and shaped into small cylinders (extrudates). As the mass comes out of the extruder, the extrudates usually break at even length due to their own weight. The granulating fluid usually serves as the binder to form the extrudate, which is usually a small strand or rod-shaped-like spaghetti. The wet extrudate is further processed in the spheronizer to form pellets. Extruders come in a variety of sizes and shapes and are usually classified according to the feeding mechanism. These include screw, gravity, and pistons to feed the wet mass into the extruder. The wet mass is essentially a wet granulation of the drug with a binder and inert excipient, which is typically a plastic deforming material like microcrystalline cellulose (Avicel). The extruder screen size directly controls the final particle size of the pellets, thus controlling drug dissolution and release.

The formulation components, amount of granulating fluid, and consistency of the wet mass can also affect the final particle size of the pellets. The extrusion speed and water content are also critical factors in achieving a desired pellet configuration. Hasznos et al. [55] have studied some factors influencing the characteristics of pellets made by an extrusion/spheronization process. They concluded that the extrusion variables are less important than granulating fluid level and spheronization parameters [55]. Goodhart et al. [56] studied the effect of extruder design on the extrusion process. The effects of granulating fluid, end plate open area, number of mixing anvils, and screw speed were evaluated, and it was found that the granulation fluid type and end plate open area had a significant effect on granulation density. Extrusion can be a batch, semibatch, or continuous process. Most pharmaceutical

TABLE 5.7
Scale-Up Parameters for Fitzpatrick Hammer Mills

	Chamber				Rotor		Machine limits		Approximate dimensions[a]		
Model	Capacity Factor[b]	Nominal Width (in.)	Screen Area (in.)	Diameter (in.)	Number of Blades	Tip Speed Factor[c]	Maximum rpm[d]	Maximum Horse Power[e]	Length (in.)	Width (in.)	Height (in.)
L1A	0.07	1	8.5	5.4	8	1.42	9000	0.5	18.5	15.4	20
Homoloid	0.4	2.5	43	6.625	12	1.73	7200	10	38	30	52
M5A	0.7	4.5	76	8	16	2.09	4600	3	32	26	55
D6A	1	6	109	10.5	16	2.75	4600	5	35	31	63
DAS06	1	6	109	10.5	16	2.75	7200	15	42	30	66
DKAS012	2.36	12	257	10.5	32	2.75	6000	30	48	32	66
FAS08	1.83	8	199	14.375	16	3.7	6800	40	60	36	72
FAS012	2.83	12	309	14.375	24	3.7	6000	75	60	36	72
FASO20	4.85	20	529	14.375	48	3.7	3000	75	60	44	72
FHASO20	4.85	20	529	14.375	48	3.7	3600	75	60	44	72
FHASO30	9.05	30	986	17.25	80	4.45	2400	150	68	60	75

Source: Courtesy of Fitzpatrick Company (Elmhurst, IL).

[a] With typical throat and 36 in. (91.4 cm) between chamber discharge and floor.

[b] Throughput relative to Model D-6 at same tip speed.

[c] Tip speed = factor × operating speed.

[d] With type 125, 225, or 425 blades.

[e] With V-belt driven at maximum rpm.

extrusion processes are batch processes. The following extrusion parameters are usually monitored and are useful during scale-up:

1. Feed rate
2. Feed temperature
3. Extrudate temperature
4. Coolant
5. Inlet/outlet temperature
6. Die temperature
7. Compression pressure

The twin screw–type extruder is available in different sizes for pilot-scale to production size batches. The rate of extrusion can range from 30 to 2000 kg/hr. Scale-up factors depend on size of extruder wet granulation final consistency.

A spheronizer is a device made up of a vertical hollow cylinder with a horizontal rotating disk. The extrudate is charged onto the rotating disk and broken into small segments, which upon further spinning on the disk, causing them to deform and form small spherical particles. The transformation of the wet mass into spherical particles is due to frictional forces between the particles and the equipment walls. Spheronization disks play an important role in the shape and size of the final spheres. Disks normally come in two types, crosshatched and radial. Radial disks are relatively faster and are commonly used. Spheronization is a batch process, the spheronized material being further dried in either fluid bed or tray dryers. The residence time in the spheronizer depends on the feed rate from the extruder. Often, the extrusion operation is a continuous one and several spheronizers are used to speed up the process. The variables affecting the overall spheronization process include the following:

1. Spheronizer size
2. Feed rate (charge)
3. Disk type and speed
4. Residence time

In general, compared with the extrusion variables, the spheronization variables affect the end product more significantly. Higher disk speed and increased residence time increase the mean diameter of pellets. This combination also tends to produce more spherical particles. Higher charge reduces moisture loss during the process and produces more plastically deformed particles. Several investigators have studied the various factors affecting the extrusion/spheronization process using factorial design and response surface methodologies [57–59]. The effect of disk speed and residence time was examined, and it was found that the friability of pellets increased with increased residence time. Increase in screen size reduces friability. Besides these variables, several formulation variables significantly control the final pellet attributes. Scale-up in the spheronization process is generally dependent on the size of the spheronizer. Demonstration of scale-up effect in extrusion/spheronization has not been thoroughly evaluated in the literature. However, the impact of scale-up is not substantial primarily due to the fact that the process is a continuous one.

Compression

Tablet compression process parameters are independent of the batch size, and large-scale batches are typically manufactured by performing compression for a longer period of time or using multiple tablet presses. Modern tablet presses are capable of self-adjustment to produce a consistent finished product during high-speed production. However, scaling up a tableting operation is still largely empirical. Scale-up parameters have been suggested in the literature based on dwell times and total work of compaction. Superior powder flow is obviously very important for producing uniform tablets in a high-speed production press. Levin [60] has identified the following critical factors that affect tablet properties due to increased compression speeds during production:

1. Decrease in tensile strength of tablets with viscoelastic materials, such as microcrystalline cellulose
2. Increased tablet friability
3. Increased tendency for lamination and capping
4. Increase in tablet temperature, which may have an impact on formulations containing materials with low melting point

In addition, several equipment parameters (differences in tablet press designs) require attention during tableting scale-up. These include capacity of the tablet press to compress to constant thickness (most commercial presses) or to constant compression force (Courtoy), method of die filling (gravity or force feeder), size of feeder chamber, and speed of the feeder motor. During formulation development, it is important to evaluate the compaction parameters of a particular formulation [61]. These would include the effect of compaction force, speed, and lubricant sensitivity of the formulation (level of lubricant and lubrication time). Formulations that are sensitive to overlubrication and also requiring a force feeder should be evaluated more thoroughly. In such instances, it is useful to estimate powder residence times inside the force feeder using Equation 5.4 as described below

$$T = 1000\ (Vd)/(wrn), \tag{5.4}$$

where T is the powder residence time in the force feeder (min), V is volume of the force feeder (mL), d is the bulk density of the blend (g/mL), w is the tablet weight (mg), r is the tablet press speed (rpm), and n is the number of stations.

The residence time of such formulations should be minimized because additional mixing inside the feed frame will adversely impact tablet hardness and/or dissolution. These trials should be performed preferably on tablet presses similar to production machines. If the tablet crushing strength declines rapidly with increasing compaction force or higher speed of compaction, the tablet may face potential capping problems during production. The rate of decrease in crushing strength with small changes in lubricant levels provides insight into the lubricant sensitivity of the formulation, which may later cause problems during production. More recently, small-scale sophisticated equipment such as compaction simulators or single-station

rotary press simulators (Presster, MCC Corporation) are available for determining various compaction parameters during trial batches. The advantage of machines such as the Presster is that they match compression forces and dwell times of any production size press and mimic its punch displacement profile. Using a Presster and the approach of dimensional analysis, Levin and Zlokarnik [62] successfully predicted parameters for scaling up from a Manesty Betapress (16 stations) to a 36-station Fette P2090 production press.

Encapsulation

Many issues important in the scale-up of the tableting operation are also important during encapsulation. Some of the problems encountered during encapsulation scale-up include powder flowability, content uniformity, plug formation and densification behavior, powder feed, and lubricant sensitivity of the blend. In addition, the type of encapsulation equipment used during development and large-scale production often dictates the success of scale-up due to differences in operating mechanisms [63]. Most equipment use the piston tamp method for plug formation along with either a dosator (MG2, Zanasi, and Matic) or a dosing disk (Hofliger–Karg). The equipment may also be differentiated based on its motion during encapsulation, such as intermittent motion machines (Zanasi E and F series and Hofliger–Karg) or continuous motion machines (MG2, Zanasi Z500 series, Farmatic). The type of production-scale equipment usually dictates the powder blend properties that need to be built into a formulation. Ullah et al. [64] evaluated the scale-up of cefadroxil encapsulation from the Zanasi LZ-64 development scale to Hofliger–Karg GFK-1500 production machine. The blend containing 1% magnesium stearate as lubricant gave satisfactory dissolution in the small batch low-speed encapsulated product but showed severe slowing down of dissolution in the high-speed production batch. Further investigation revealed that the powder tamping process used in the high-speed machine exposed the powder to additional shear forces, causing overlubrication and resulting in slower dissolution. It was concluded that reducing the amount of magnesium stearate to less than 0.6% resulted in a powder blend less prone to shear effects in the large-scale encapsulation process [64].

Pan Coating

Coating is typically the last step in the production process for tablet dosage form. Coating performance can significantly affect the appearance of the finished product and other quality attributes influencing the drug release and in vivo performance. Although sugar coating and microencapsulation approaches are available, film coating using perforated pan and air suspension techniques are the most popular and will be the focus of this section. Coating serves many purposes, including taste masking, improving product appearance, light and moisture protection, and controlled release (enteric or sustained release). Several water-soluble and water-insoluble polymers and ready-to-use coating systems are commercially available. In recent times, water-based aqueous systems have gained in popularity due to environmental issues related to the use of organic solvents. However, for certain applications, organic coatings may be the only alternative.

Tablet coating in the batch approach uses some variations in a perforated pan equipped with a special air handling system and coating guns. Campbell and Sackett [65] have identified several key parameters affecting the film coating process in a perforated pan:

1. Process airflow and evaporation rate
2. Inlet/exhaust temperature
3. Spray rate, number of guns, spray pattern, and achievable droplet size
4. Pan speed
5. Atomization air pressure
6. Product load and gun to bed distance

Pans may be partially perforated (Hi-Coater [Vector/Freund] and Driacoater [Driam]) or fully perforated (Procoater [Glatt], Fastcoat [O'Hara], and Accela Cota [Thomas Engineering]). Many of these machines are available from small laboratory scale to production size equipment. Table 5.8 summarizes the dimensions and brim volumes for Vector Hi-Coater pans available in production sizes. One of the important factors governing the scale-up of the film coating process is the evaporative capacity of process air. Equation 5.5 is useful in estimating this evaporative capacity during scaling up [65]:

$$R = \frac{\text{CFM} \times C_p \times d \times \text{min} \times [(T_{in} - T_{out}) - H_L(T_{in} - T_{out})]}{\text{LHV}}, \tag{5.5}$$

where R is the evaporation rate of water (lb/hr), CFM is the actual process airflow (ft^3/min), C_p is the specific heat capacity of air (0.241 Btu/lb m°F), d is the density of air (0.0634 lb m/ft^3), min is the number of minutes per hour (60 min/hr), T_{in} is the process inlet temperature, T_{out} is the process outlet temperature, H_L is the percent heat loss of the system, and LHV is the latent heat of vaporization of water (1040 Btu/lb m).

TABLE 5.8
Standard Hi-Coater (Vector Corporation) Production Coating Pan Specifications

Model	Pan Diameter (in.)	Brim Volume (liters)	Number of Spray Guns	Process Air CFM Range	Overall Dimensions (in.) (W × D × H)
HC-100	39	90	2–3	530–880	55 × 63 × 69
HC-130	52	225	4	765–1275	65 × 68 × 80
HC-150	59	350	4	1016–1690	70 × 78 × 89
HC-170	67	550	4–6	1270–2120	81 × 88 × 99

Source: Courtesy of Vector Corporation, Marion, IA.

TABLE 5.9
Scale-Up Considerations in Pan Coating

Parameter	Scale-Up Equation
Batch size	$Batch\ size\ (L) = \frac{Batch\ size\ (S)}{volume\ (S)} \times volume\ (L)$
Pan speed	$Pan\ speed\ (L) = \frac{Pan\ diameter\ (S)}{Pan\ diameter\ (L)} \times pan\ speed\ (S)$
Spray rate = gun	Assuming same gun to bed distance
Spray time	$Spray\ time\ (L) = Spray\ time\ (S) \times \frac{batch\ size\ (L)}{batch\ size\ (S)} \times \frac{spray\ zone\ (S)}{spray\ zone\ (L)}$
Airflow	$Airflow = \frac{total\ spray\ rate\ (L)}{total\ spray\ rate\ (S)} \times airflow\ (S)$

Source: Sackett, G. BASF = Vector Coating Seminar Notes, Vector Corporation, Marion, IA. www.vectorcorporation.com.
Note: L = large coating pan; S = small coating pan.

Sackett [66] has discussed in detail the factors governing scale-up of a pan coating process, and these are summarized in Table 5.9. Usually, scale-up involves increasing the spray rate with a corresponding increase in the pan speed. However, in such circumstances, tablet attrition and overwetting should be closely monitored.

Fluid Bed Processing

Fluid bed or air suspension coating is a more complicated process and requires additional parameter optimization compared with pan coating. Air suspension coating can be broadly classified into three types of processes: (1) top spray, (2) rotary fluid bed with tangential spray, and (3) Wurster/bottom spray [67]. Top spray is well suited for large-particle coating, whereas rotor and Wurster processes are suitable for fine-particle coating and drug layering onto nonpareil seeds. Operating parameters important in pan coating such as process airflow (fluidization), inlet/outlet temperatures, and spray rate are also important for air suspension coating. Besides factors such as rotor speed in rotary fluid bed, partition height and distribution plate inside the Wurster column play a critical role in scale-up [68,69]. A summary of scale-up parameters and other considerations during air suspension coating is presented in Table 5.10. Table 5.11 summarizes the technical specifications for laboratory-, pilot-, and production-scale GPCG series fluid beds from Glatt.

A fluid bed technology based on a different operating principle is offered by Huttlin (Bosch Huettlin GmbH, Schopfheim, Germany). The three-in-one fluid bed, Huttlin Dryer-Granulator-Coater (HDGC) allows drying, granulating, and coating on the same machine using a single product bowl [70]. The Huttlin fluid bed technology minimizes drying, granulating, and coating time and provides several

TABLE 5.10
Scale-Up Considerations for Air Suspension Coating Processes

Parameter	Scale-Up Equation
Batch size	Top spray and rotary processes: $Batch\ size\ (L) = \frac{volume\ (L)}{volume\ (S)} \times batch\ size\ (S)$
	Wurster process: $Batch\ size = product\ bulk\ density \times [column\ volume - (number\ of\ partitions \times volume\ of\ partitions)]$
Fluidization air volume	$Air\ volume\ (L) = air\ velocity\ (S) \times cross\ sectional\ area\ (L)$ $Air\ velocity\ (S) = air\ volume\ (S)/cross\ sectional\ area\ (S)$
Spray rate	$Total\ spray\ rate\ (L) = spray\ rate\ (S)/gun \times \frac{number\ of\ guns\ (L)}{number\ of\ guns\ (S)}$
Rotor speed	Rotor process: $Rotor\ speed\ (L) = rotor\ speed\ (S) \times \frac{rotor\ diameter\ (S)}{rotor\ diameter\ (L)}$

Source: Sackett, G. BASF/Vector Coating Seminar Notes, Vector Corporation, Marion, IA. www.vectorcorporation.com.
Note: L = Large fluid bed system; S = small fluid bed system.

advantages relative to the traditional fluid bed process. Compared with the traditional fluid bed process, the Huttlin fluid bed technology enables the operator to prepare denser and more uniform granules and provides the ability to coat small beads and powder particles (as small as 5 μm) with high efficiency and with minimal agglomeration. It does not use any bottom mesh or any moving parts such as a rotor. This advance in fluid bed technology provides the following unique features address the shortcomings of the traditional fluid bed dryer, top spray granulation, or Wurster coating technologies:

1. A disc-jet bottom air distribution (stationary) plate with 3 ± 0.5% opening generates a high-pressure differential to accelerate the velocity of process air passing through the air distribution slots cut at a 45° angle with 200 μm on top and 300 μm underneath. The process air flows at a 45° angle through the plate at high velocity, generating a uniform and constant circular movement of the product while keeping the product fluidized at a fairly low height. The circular motion of the product helps to complete both processes rapidly while ensuring that no product falls through the air distribution slots. The process airflow is always switched on during loading and unloading of the product.
2. The fluid spray nozzles for both spray granulation and coating processes are mounted at a 45° angle through the air distribution plate to ensure a

TABLE 5.11
Specifications for Selected GPCG Fluid Bed Systems from Glatt

GPCG Model #>	3	5	15	30	60	120	200
			Maximum working volume of product container				
Top spray (liters)	5	22	45	100	220	420	670
Wurster HS[a] (liters) (size)	5.4 (7″)	6.3 (7″) 14 (9″) 38 (12″)	14 (9″) 38 (12″) 102 (18″)	38 (12″) 102 (18)	120 (18″) 417 (32″)	417 (36″)	417 (32″) 820 (46″)
Rotor (liters) (size)	4.5 (300 mm)	30 (480 mm)	30 (480 mm)	60 (620 mm)	60 (620 mm) 105 (790 mm)	105 (790 mm) 180 (1000 mm)	180 (1000 mm)
			Inlet air handling unit				
Heating capacity (kW)	10.5	22	44	86	132	174	227
Temperature range (°C)	0–100	−10 to +60	−10 to +60	−10 to +60	−10 to +60	−10 to +60	−10 to +60
Steam consumption[b] (kg/hr)	18	37	75	147	226	297	389
			Exhaust air fan				
Capacity (kW)	2.2	5.5	7.5	15	22	30	37
Air volume[c] (m^3/hr)	200	1000	1500	3000	4500	6000	8000
Differential pressure[c] (mm/WG)	800	1000	1000	1000	1000	1000	1000
			Maximum air consumption of atomizing nozzle				
Top spray (m^3/hr)	22	25	25	30	30	30	95
Wurster HS (m^3/hr)	9	25	70	70	210	210	210
Rotor (m^3/hr)	9	25	25	30	30	60	60

Source: Glatt Air Techniques (Binzen, Germany).

[a] Excluding volume in partition.

[b] At 30 bar saturated pressure.

[c] At 20°C and 1013 mbar.

concurrent direction of spray and process air as well as minimize the distance between spray nozzle and fluidized product. The special nozzle is designed without any needle or moving mechanical parts and receives the spray liquid through a dedicated peristaltic pump head to assure a constant delivery.

3. The dynamic process filters are constructed with an inner conical part, which allows for an extra 40% surface area for drying and spray granulation processes. The filter socks (typically five or six depending on machine size) are blown back in sequence throughout the process. There is always one sock being blown back, whereas the remaining four or five are in use, constantly filtering process air. This allows for a constant airflow throughout the process with no intermittent disruption due to filter cleaning.

Scale-up of particulate or pellet coating in the fluid-bed remains a challenging task in today's pharmaceutical processing. The challenge in scale-up lies in the making of a uniform film (for controlled drug release) onto small particles in a dynamic environment comparable to the laboratory-scale batch. Because microparticle coating is a continuous and simultaneous mass and heat transfer process, the coating dispersion spray mechanism, fluidization of the substrate (microparticles), airflow, and heat distribution in the coating environment are critical to the overall process. The scale-up process requires careful consideration of multiple processing parameters such as (a) batch size relative to the equipment size (% load), (b) product bed temperature (inlet, outlet temp), (c) airflow and flow pattern (CFM), (d) spray rate and spray pattern (gun opening, droplet size), supply air humidity (dew point), etc. A computer program developed by Huttlin takes critical process variables from the laboratory scale and generates optimal working ranges for these parameters in the large-scale equipment to achieve comparable coating environment. This computer-aided scale-up process enables a development scientist to achieve the end product (dry granule, drug-loaded seeds, coated particles/seeds) comparable with the laboratory-scale batch with a high degree of assurance. The technology considers three critical parameters as described below:

1. The large-scale equipment uses air velocity through 45° angle slits similar to the small-scale equipment. However, the air volume (m^3/hr) is significantly increased to maintain the drying efficiency. For example, both the laboratory-scale unit (Unilab [for ~2.5 kg batch]) and the production unit (HDGC-200 [for 120 kg batch]) maintain the uptake air velocity of approximately 1 m/sec for an air volume of 250 and 2290 m^3/hr, respectively. The air volume is not increased in proportion to the batch size (load). The drying energy supply from relatively lower proportion of total air volume is compensated by an increase in inlet temperature without increasing the bed temperature. The inlet temperature requirement is calculated by a scale-up factor in the program integrated into the Huttlin equipment.
2. Film formation (coating) in the large-scale-up batch is maintained comparable with the small-scale batch by maintaining the coating dispersion spray rate (g dispersion per min/kg substrate). This is achievable due to an increase in the number of spray heads in the larger machine. For example, a batch of

approximately 2.5 kg microparticles coated in the laboratory-scale machine (Unilab with two spray nozzles using 15 g/min × 2 guns) can be scaled up to a batch of 120 kg in a production size fluid bed HDGC without a significant increase in the same spray rate per gun. The HDGC-120 is equipped with 12 spray guns to accommodate the delivery of higher amounts of spray for a larger batch. This is in contrast to the traditional fluid bed equipment that is designed with a fewer number of spray guns and can only accommodate higher spray rate by delivering a higher amount of dispersion through the nozzles. To permit higher spray rates, these nozzles must use a larger nozzle diameter and increased atomization air that can contribute to changes in spray droplet size and plume geometry, thereby influencing the dynamics of film formation during scale-up.

3. Huttlin's laboratory-, pilot-, and large-scale commercial fluid bed equipment use the same nozzle sizes. The spray nozzles are mounted at a 45° angle through the air distribution plate, ensuring a concurrent direction of spray and process air as well as minimizing the distance between spray nozzle and fluidized product. The identical spray nozzle is used for both spray granulation and fine-particle coating processes. The nozzle is designed without any needle or moving mechanical parts, and the spray liquid supply for each nozzle goes through a dedicated peristaltic pump head for accurate delivery of the spray liquid. Compressed air is used for atomization, which determines droplet size and "microclimate air," which blows a protective ring of air around the tip of the nozzle to prevent any blockage and also helps in developing the desired droplet size by deflecting the fluidized product at the required distance.

Process Demonstration and Technology Transfer

The formulation and process developed at a small scale must be capable of producing the same product using the same process at a larger scale. Manufacturing parameters that affect the quality attributes of the in-process and finished product should be identified. These parameters are to be studied to demonstrate the boundaries of the manufacturing process controls. Statistically designed pilot-scale batch experiments provide valuable information from a limited number of trials to predict the flexibility and constraints to be applied to the scale-up batch.

Process Demonstration

Process demonstration shows that the process utilized in the pilot plant is capable of producing the desired product at a larger scale. The demonstration batch may be an experimental large-scale batch or a bio/stability batch that may or may not be the actual production size batch. In the generic industry, several factors such as complexity of the process, in-house expertise, availability of the API, cost, and timeline are considered in the planning for a process demonstration batch. Product development personnel in collaboration with production and validation personnel manufacture the batch. All important aspects of the process (mixing times, granulation endpoints, drying curves, moisture contents, compression forces, coating parameters, etc.) are carefully explored

and monitored. After completion of the batch, a meeting among the development, manufacturing, and validation groups is useful to discuss the process and product performance. Based on the outcome of the batch and input from various experts involved, any changes or modifications can be made before the biobatch. Production personnel are thus thoroughly aware of CPS and successful execution of future batches is assured.

Technology Transfer

Technology transfer involves transferring the product knowledge, development experience, product manufacturing technique, and responsibilities from the development group to the regular production group. The technology transfer plan and performance vary widely among the generic companies. In many firms, there is no formal technology transfer procedure, and in others, it is poorly managed. This may lead to failed PPQ, manufacturing problems difficult to correct during the product launch, and delays the marketing of the product. Involvement of production personnel in the research batches should start as early as the process demonstration batch as mentioned above. Biobatch manufacturing in the production floor serves a beneficial step in technology transfer. The process validation/technology transfer group in conjunction with the development, analytical, manufacturing, quality assurance (QA), and packaging groups prepares a technology transfer document. This document should include information on the following:

1. Formulation and process development studies and knowledge generated during development
2. Relevant analytical methods and data
3. Manufacturing master formula and process flow chart
4. Monographs of all excipients and the final product (if available)
5. Description of packaging components
6. Cleaning methods and criteria
7. PPQ protocol
8. Resource requirements and timeline

It is important for the development team to discuss all aspects of the manufacturing process and resource requirements with relevant departments. The manufacturing process, process controls, in-process sampling and testing specifications, and equipment operation, especially in the case of new technology, are to be explained to the manufacturing personnel. A clear understanding of various steps of the manufacturing process as identified in the manufacturing master batch record is essential. Several critical steps and parameters need to be addressed, for example, addition of the granulating fluid to a high shear mixer can be done for a fixed time or fixed rate, or by defining granulation endpoints such as impeller torque or power (kW). Often, the order of addition of a particular ingredient or bulk drug component to the blender is important. In-process sampling procedures, such as granules for moisture content during drying or powder blend for content uniformity, should be clearly stated. The technology transfer completes with the successful completion of three consecutive PPQ batches. All documents including executed manufacturing masters, test results, out of specification (OOS) values (if any), deviations (if any), and investigations (if any) should be

compiled as formal reports. The report must include explanation for any OOS values and sound corrective action from both technical and compliance points of view.

In the current pharmaceutical industry, technology transfer may have to take place across plants, companies, and possibly across countries. These types of transfers pose significant additional challenges not only limited to differences in company cultures, local requirements, labor laws and regulations, requirement for licenses and permits, differences in languages, time zones, national norms, and best practices. Similar challenges are also encountered with product and technology transfers to support acquisitions, mergers, plants, and capacity optimizations.

Computer System Validation (CSV)

CSV is the result of applying all validation concepts to computer systems associated with process and packaging and is defined as "establishing documented evidence, which provides a high degree of assurance that a computer system will consistently produce results that meet its predetermined specifications and all quality attributes."

Examples of computer systems include (a) automated manufacturing equipment; (b) control systems; (c) automated laboratory equipment; (d) laboratory data capture systems; (e) manufacturing execution systems; and (f) computers running laboratory, clinical, or manufacturing database systems.

There are two main reasons why CSV is extremely important in the pharmaceutical industry: (a) systematic CSV prevents the software problem reaching the production environment and (b) FDA regulations mandate the need for CSV. The FDA has published two guidance documents related to software validation and electronic records [71,72]. In addition, a recently published book authored by Wingate discusses CSV and associated risk management and regulatory compliance [73].

Two recent white papers, (1) Good CSV Practice and (2) Risk Assessment for Regulated Computerized Systems, provide a good overview of CSV. The first white paper provides an overview of CSV to those involved with computer systems in the pharmaceutical industry. It describes the definition of CSV, its potential benefits, frequency of validation, personnel required, and an overview of methodology employed [74]. The second white paper describes the process followed by ps_testware during risk assessment intended to target validation efforts for cGxP and Part 11 regulated computer systems. These are available online at and are published by ps_testware. This group also offers training, consulting, coaching, assessment, planning, and implementation of CSV programs [75].

In addition, the Institution of Validation Technology Standards Committee has also proposed Validation Standards related to CSV. This standard is useful for practitioners worldwide who develop, implement, validate, and maintain systems used to automate manufacturing processes or to otherwise influence the ultimate quality, safety, or efficacy of drug substances or drug products. The focus of these standards is the pharmaceutical industry [76].

Process Performance Qualification

The 2011 Guidance–Process Validation: General Principles and Practices aligns process validation activities with a product lifecycle concept and the ICH Q8, Q9,

and Q10 guidelines described earlier [77]. The new guidance recognizes the need for QbD tools and quality risk assessment from the product development stage through commercial manufacturing and continuous improvement. It moves away from the old approach of validation by producing three consecutive batches meeting specifications to one of increased process understanding and control of variability. Process validation for solid oral dosage forms in the generic industry is required by the current Good Manufacturing Practices (GMPs) for finished pharmaceuticals [78]. According to the FDA's Guidance [77], validation is defined "as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."

As per the new guidance, process validation encompasses three stages:

Stage 1: Process Design

This stage is whereby process knowledge and understanding is gathered through development and scale-up activities. The commercial manufacturing process is defined during this stage and a strategy for process control is outlined. At this stage, process design experiments may be performed under non-GMP conditions; however, they should be based on sound scientific principles. Use of DOE, simulations, and risk analysis is recommended. Early product development activities provide key inputs to the process design stage. Proper documentation should be provided at this stage identifying the decisions made about the process, especially the variables studied for a unit operation and the rationale for those variables identified as critical or significant. Process knowledge and understanding gathered during this stage also forms the basis for establishing process control. Controls can include product and equipment monitoring and may include Process Analytical Technology tools.

Stage 2: Process Qualification

This stage of PPQ scientifically establishes that the process is capable of reproducibly manufacturing the commercial product consistently meeting predefined quality attributes. In addition. the product and process are expected to consistently meet the specifications and acceptance criteria where variability is measured. These activities are performed under GMP-compliant procedures. There are two elements to this stage: (a) design of facility and qualification of utilities and equipment, including installation qualification (IQ) and operational qualification (OQ), and (b) PPQ.

Equipment Qualification

Equipment and utilities qualification is an important part of the overall validation program. Qualification for new equipment or a new facility incorporates extensive testing, verification, and documentation to establish that a particular piece of equipment meets the design specifications and its installation is appropriate to execute the functions required. The procedures involved not only assure the current state of the equipment but also help maintain them in peak working condition and calibration status.

Before performing IQ, a prequalification is done to assess the vendor specifications and process and product requirements of the equipment. Once the decision is

made to purchase the equipment, preparations are made for IQ in consultation with the vendor and the engineering department. The plant engineering department is responsible for designing the working area as per the manufacturing requirements and the necessary utilities. As the equipment is installed, each of its components is qualified to perform according to the vendor's specifications. All vital gauges, charts, recorders, and displays are calibrated and appropriate calibration schedules are established. The validation department is responsible for coordinating all the documentation related to the installation, including the operating manuals, technical drawings, calibration requirements, certificates, and standard operating procedures (SOPs). When compiling such documentation, the validation personnel should perform extensive testing of the equipment and should not rely solely on the vendor's claims. The equipment is usually assigned a serial or asset number at this stage. Once the equipment is installed, an OQ is performed using a written protocol to ensure that the equipment performs within the specified limits when operated using approved SOPs. Such OQ studies are usually performed using placebo batches and may involve the combined technical expertise of the production, validation, and engineering departments and also the equipment vendor. Performance qualification (PQ) on new or existing equipment is done to assure that it is working up to the appropriate level, in reproducing a particular process or product, within predetermined specifications.

Process Performance Qualification

PPQ combines the facility, utilities, equipment with trained manufacturing personnel, control procedures, and components to produce commercial batches. The term PPQ can be considered analogous to the traditional "process validation" because multiple batches are made at the commercial scale. The new guidance does not explicitly state the use of three consecutive commercial-scale batches for this purpose. In practice, this may mean that three batches may be sufficient to provide data to assure that the process is adequately qualified or may be more than three batches are required for this purpose.

PPQ establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product (CQAs) while preventing undesirable properties. It involves systematic work and documentation of performance so that the crucial parameters in the pharmaceutical manufacturing process will consistently produce a quality product. Although PPQ features in the final stages of product and process development, several validation concepts are incorporated in the laboratory/pilot-scale development, scale-up, and process characterization stages. Typically, for generic solid dosage forms, an integrated team of members from formulation development, process engineering/technical operations, analytical chemistry, manufacturing, and QA are involved at this stage. Depending on the complexity of the manufacturing process, several equipment, process, and product parameters are optimized at a smaller scale compared with the production size batch. Once the formulation composition and manufacturing process are optimized at the smaller scale, the next stage involves characterizing the process at a larger scale, usually using production equipment. At this stage, the experience and input of the production personnel are vital for the success of the project. During

this process, the process is challenged at the "bookends" of the proposed parameter ranges and necessary adjustments made if required. Depending on the pharmaceutical unit operations (dry blending, wet granulation, milling, roller compaction, compression, encapsulation, coating, etc.), several CPPs are varied, whereas the product properties are measured and evaluated thoroughly (refer to Table 5.2 above for typical evaluation parameters). In most cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of the process compared with routine commercial production.

The formal PQ process may begin during the manufacture of the biobatch if the intended production batch size is the same. The objective is to qualify the process using full-scale production equipment. The PPQ is performed as per a written and approved PPQ protocol defined by the FDA guideline as follows: "A written protocol that specifies the manufacturing conditions, controls, testing and expected outcomes."

A well-written protocol forms the backbone of the validation plan and should include the following items:

1. Purpose of the study
2. Personnel responsibilities
3. Equipment qualification status
4. Critical process steps (CPS)
5. Critical process parameters (CPPs)
6. Sampling plan
7. Testing plan
8. Acceptance criteria
9. Process capability analysis
10. Success criteria

In the manufacture of solid dosage forms, depending on the complexity of the manufacturing process, several process parameters may be specified for testing. For general guideline for process and product parameter inclusion in the PPQ protocol, refer to Table 5.2. The amount and number of samples collected and tested will depend on the type of manufacturing process used, for example, blend content uniformity to validate a blending operation or dissolution profile to validate tablet hardness range. Mixing of powder components is probably the most common manufacturing step in pharmaceutical industries. The mix uniformity of the blend is evaluated from samples that itself may contribute to the outcome of the result due to variation in the sampling procedure, device, amount of sample, etc. The problem in blending validation due to sampling error has been investigated with various recommendations [79–86].

This protocol-driven PPQ usually forms part of what is termed as prospective PPQ. Here, the PPQ is conducted before the distribution and sale of a new generic product or an existing product manufactured with a revised process, which can affect the product or quality attributes of the finished product. Many companies validate their manufacturing process well ahead of approval, if the risk is considered minimal

and if it is expected that the FDA review letter will not challenge the process or product specifications. A second option of concurrent PPQ is used to enhance or refine acceptance criteria for in-process control. This type of validation is used, with special justification, for products with low market volumes (e.g., radiopharmaceuticals) and products that may be facing short supply. In such special situations, the PPQ protocol may be designed to release the PPQ batches for commercial distribution before complete execution of the protocol (i.e., concurrent release). The last option of PPQ is revalidation and is used when changes in process equipment or manufacturing site occur or if the process drift warrants it. Usually, these changes are deemed major or minor as per the "scale-up and post-approval changes" guidelines and a decision is made requiring revalidation.

The execution of the PPQ protocol begins after it has been reviewed and approved by all relevant departments, including QA. During the manufacturing process, several samples are collected as per predefined sampling protocol and tested using approved and validated analytical methods. These validation studies are thoroughly documented and summarized in a report. The PPQ report should include the following items:

1. Discuss and cross-reference all aspects of the PPQ protocol.
2. Summarize and analyze the data as specified in the protocol.
3. Evaluate unexpected observations and additional data not specified in the protocol.
4. Discuss and summarize all nonconformances encountered during the manufacturing process and any other relevant information that could impact the validation.
5. Provide details on any corrective action or changes that need to be made to existing procedures or controls.
6. Infer clear conclusions about the ability of process to meet established criteria as per the protocol and whether it is in a state of control. This should include proper documented justification for the approval of the process to produce the commercial product and the entire compilation of the process knowledge and understanding gained from process design through process qualification stages.
7. Review and approve the report by all relevant departments, including the QA unit.

The manufacturing process and testing is approved for regular production after careful evaluation of the successfully completed PPQ documentation.

Stage 3: Continued Process Verification

The manufacturing process is continually monitored and attempts are made to reduce product and process variability. An ongoing procedure for data collection from every batch should be established. Statistical analysis should be performed to identify any data trends. Maintenance of the facility and equipment through monitoring and

routine calibration procedures also occur as long as the product is commercialized and additionally ensures that the process remains in control.

Documentation

Documentation is an important aspect of the scale-up, technology transfer, and PPQ. Hence, it becomes imperative that all relevant documents pertaining to the manufacturing, testing, and releasing of the bio/validation batch are compiled and organized before a preapproval inspection. The documents should be checked for data accuracy and adequacy as required by the FDA's guidelines. Documentation covering the items below should be compiled in a timely manner:

1. Executed masters for the bio/submission batches
2. Test results, including OOS values, repeat testing, etc.
3. Deviation and OOS investigations, findings, and conclusions including corrective and preventing actions
4. Equipment IQ, OQ, and PQ
5. Cleaning validation
6. Change control documentation
7. Related SOPs
8. Product launch batches (including any scale-up batches)

All documentation related to active and inactive raw materials, including test methods, vendor's certificates of analysis, BSE/TSE certifications, and quality-control release specifications, are included. The original batch manufacturing records, analytical method validation reports, equipment IQ/OQ, PPQ documents, production personnel training records, and equipment maintenance records form the main sections of a project documentation file.

CONCLUSION

Scale-up, technology transfer, and PPQ are conducted at the late phase of product development. However, the performance of these steps is largely dependent on the product composition and process selected in the early phase of development. The technology chosen at an early developmental stage and employed for manufacture of the biobatch remains with the product during its lifecycle. During this early phase, the development scientist must consider the future demand for the product in selecting the product components, process, and equipment. In reviewing and selecting the formulation composition and manufacturing process, it is important to consider the critical physicochemical properties of the drug and excipients along with equipment capabilities and limitations. All equipment should be qualified for installation, operation, and performance before the biobatch. The biobatch should be evaluated for process performance. All operational documents and test results generated from the biobatch must be reviewed before initiating further scale-up and/or technology transfer. A team effort among formulation, validation, production, analytical, and logistic support groups is crucial to the success of scale-up and technology transfer resulting in a successful PPQ.

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6 Drug Stability

Pranab K. Bhattacharyya

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INTRODUCTION

In 1984, the Hatch–Waxman Amendment of the Federal Food, Drug, and Cosmetic Act (the Act) was enacted. This amendment, which is also known as the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417), allowed lower priced generic drug equivalents of the off-patent branded drugs in the US marketplace. In this chapter, the US Food and Drug Administration (FDA) requirements governing the stability of generic drugs will be discussed. Stimulated by the growth of the generic industry, a comprehensive journal publication [1] devoted exclusively to the development, manufacturing, quality control, and quality assurance of generic drugs is available in print and on the website.

Why Stability for Generic Drugs?

A generic drug [2] is equivalent to the corresponding branded drug with respect to the active pharmaceutical ingredient (API), strength, dosage form and dose, route of administration, safety, efficacy, and label claim. Generic and branded drugs may, however, differ with respect to inactive ingredients, such as lactose and magnesium stearate, which are necessary to formulate the drugs, for example, as tablets and capsules.

When a formula for a generic drug has been finalized for an off-patent branded drug, the generic drug manufacturer is required to conduct certain studies and submit an abbreviated new drug application (ANDA) to the Office of Generic Drugs (OGD) of the FDA to demonstrate its bioequivalency and quality. Proof of bioequivalence is established through an appropriate comparative bioavailability (bioequivalence) study, which is discussed in Chapters 10 and 11. Drug quality, on the other hand, is demonstrated through implementation of extensive analytical testing procedures. The analytical testing methodologies and data are described in the Chemistry, Manufacturing, and Controls section (CMC) section of the ANDA application, which are covered in Chapters 3 and 9.

A key component of drug quality is its stability profile, which is an integral part of the Chemistry, Manufacturing, and Controls section. Drug stability is characterized by parameters such as identity, assay, degradation profile, and dissolution rate. A drug is stable when these quality characteristics remain within predetermined quality-control specifications for at least the duration of the expiration period. A stable generic drug, which has been shown to be bioequivalent to a branded drug, assures that it continues to be safe and efficacious throughout its shelf-life. Assessment of the stability of drugs is also mandated by the Code of Federal Regulations, Title 21, Part 211.166 (usually abbreviated as 21 CFR Part 211.166).

Terminology

In the pharmaceutical industry, the terms active pharmaceutical ingredient or API, drug substance, active ingredient, active substance, or simply active or drug are all used interchangeably. Drug products or drugs or products or finished products are also interchangeable. The term shelf-life is used interchangeably with expiration dating period, expiration period, expiration dating, or expiration date. An excipient is any inactive substance other than the drug substance used in the corresponding drug product.

API STABILITY

The development of the stability profile of an API is a prerequisite for approval of an ANDA application. Analytical testing to establish an API's stability profile is usually conducted by its manufacturer. Critical stability parameters include physical appearance (e.g., whether crystalline or amorphous powder for solid APIs), color, assay, degradation profile, and hygroscopic tendency. The API manufacturer's Drug Master File (DMF) submission to the FDA will not be complete without stability data. In practice, the review of the DMF by the FDA is triggered upon the submission of an ANDA application referencing the DMF.

Pharmacopeial and Nonpharmacopeial APIs

Currently, a large number of APIs are already included in the United States Pharmacopeia (USP) and its supplements. It is known that a vast majority of the pharmacopeial-grade APIs that are used by generic manufacturers are produced

in foreign countries, such as Ireland, Italy, India, and China, among others. It is a requirement that all manufacturers of APIs have modern production facilities that are staffed with well-qualified personnel and have implemented good quality systems that conform to the U.S. current good manufacturing practice (CGMP) requirements. Over the years, the foreign inspections branch of the FDA has done a truly outstanding job through vigorous inspections in enhancing the CGMP systems to the point that the foreign manufacturers offer high-quality APIs and an excellent value for the US as well as global markets. Through inspectional observations and, when/where necessary, warning letters, the FDA ensures that only manufacturers who have implemented adequate quality systems and manufacturing technology to comply with CGMP requirements can supply APIs to the U.S. drug product manufacturers.

Many APIs for generic drugs, however, are still not listed in the USP. Various API monographs are currently going through the review process in the Pharmacopeial Forum. CGMP requirements are nevertheless equally applicable regardless of whether the APIs are in the USP or not. The API manufacturers seem to be cognizant that demonstration of stability profiles of APIs are an essential component in meeting these requirements.

Specifications and Test Methods

For those APIs with monographs published in the USP, the API manufacturers must ensure that their specifications are not wider than the pharmacopeial specifications. The specifications must be either identical or tighter than the respective pharmacopeial specifications. Historically, third-world countries in Asia and Africa have followed the USP. European countries and Japan have their own compendia, such as the European Pharmacopeia (EP) and Japanese Pharmacopeia (JP). Because foreign manufacturers are known to produce APIs for international markets, they have focused on developing a single set of specifications with the tightest limits to meet the requirements of the major pharmacopeias (USP, EP, JP). To assure that an API meets the stability specifications for international markets, the tightest specifications included in the major pharmacopeias should be selected. For example, if the USP has specifications of 98.0% to 102.0% for assay and 0.2% for a degradant and other pharmacopeias have specifications of 99.0% to 101.0% and 0.3%, respectively, the tightest specifications of 99.0% to 101.0% and 0.2% should normally be set as the stability specifications for the API.

For USP-grade APIs, USP test procedures should be followed. If an API manufacturer's test method differs from the USP procedure, crossover studies are required to demonstrate equivalency between these procedures. For example, if a titration procedure is employed by the manufacturer and a high-performance liquid chromatography (HPLC) procedure is described in the USP for an assay, the API sample should be analyzed by both methods. Another possible scenario is that an HPLC method may be used for the determination of impurities and degradants by the API manufacturer, which may be different from the HPLC method listed in the USP. Results from the two HPLC methods should be comparable within the experimental errors of the methods. This will allow the use of the titration procedure by the API manufacturer for assay and its HPLC procedure for stability testing and at the same time permit

labeling the API as conforming to USP. The situation becomes complicated if the different pharmacopeias employ different methods of analysis. In that case, multiple crossover studies should be conducted to allow the use of a single test method by the API manufacturer for the analysis of a given test attribute such as assay.

To harmonize development of specifications for impurities and degradants in ANDAs and DMFs, the FDA has published a guidance [3] to provide recommendations on the identification and qualification of impurities in APIs produced by chemical synthesis, which are applicable for both pharmacopeial and nonpharmacopeial APIs.

FDA and ICH Guidelines

Both FDA and ICH (i.e., International Conference on Harmonisation) guidelines [4–8] require stability-indicating assay procedures for analysis of drugs. The HPLC assay procedure is the preferred method for stability testing. For demonstration of stability, an API sample is purposely degraded [6] by stressing it under harsh conditions of temperature, humidity, oxidation, ultraviolet (UV) light, acidity, and basicity. Evidence for the stability-indicating property of the assay procedure is demonstrated by adequate separation of the degradants from the active ingredient peak. To assure that no degradants are coeluting with the active peak, it is advisable to conduct peak purity studies by multiwavelength scans of the chromatographic peak using a photodiode array detector (PDA). With this technique, the purity of the main peak can be established only if the UV chromophores of the API and the coeluted degradant are sufficiently different. However, if the UV chromophores are similar, this technique will not succeed in establishing peak purity. In such cases, the more powerful hyphenated technique of HPLC analysis coupled with mass spectrometric detection (known as liquid chromatography-mass spectrometry or LC-MS) should be considered.

Issues for Multisource APIs

Spurred by the growth of the generic industry, multiple manufacturers of APIs have arisen. With time, many more API manufacturers will gain FDA approval and join the ranks of producers of quality APIs. Because they will all compete for essentially the same generic market for a given API, their success will be governed by their ability to deliver quality APIs at the least possible cost. This will require creativity for the API manufacturers to survive and succeed in a highly competitive business. For that to happen, they will have to cut costs in the production of the APIs. The different manufacturers will employ different syntheses for the same API. In all cases, the final product, the API, must be chemically identical. The starting chemicals, intermediates, final intermediates, synthetic pathways, and residual solvents detectable in the API will usually differ from one manufacturer to another. Although the API produced by different manufacturers must be chemically indistinguishable, its physical properties such as bulk density, particle size profile, its crystalline or amorphous character, and its rate of degradation may differ. Therefore, in addition to cost, its stability as well as its processing characteristics in the manufacture of finished products should be considered in selecting the manufacturers of the APIs.

Method Validation

Analytical methods for stability testing of APIs should be validated. USP contains a General Chapter <1225> on methods validation [9]. The FDA has also posted the ICH guidelines, Q2A and Q2B, on the validation of analytical procedures on its website [10,11]. These and other FDA guidelines [12,13] should be considered in developing and implementing a methods validation protocol for an API. In the USP, validation of an analytical procedure is defined as the testing process by which it is established that certain performance characteristics are achieved. Typical performance characteristics in the USP and ICH for the validation of analytical methods include the following: accuracy, precision, specificity, detection limit, quantitation limit, linearity, and robustness. The definitions for these analytical performance characteristics are provided in the USP and ICH guidelines and are not covered in this chapter. It should be noted that validation is a dynamic process and should be repeated when an analytical method has been revised or when an API is procured from a different manufacturer or produced by a different synthetic route.

Shelf-Life Development and Assignment

Stability testing should be conducted with the API packaged and stored under the ICH accelerated and long-term stability conditions, which are listed below

Accelerated stability condition: 40 ± 2°C/75 ± 5% RH
Long-term stability condition: 25 ± 2°C/60 ± 5% RH

For stability testing, samples may be stored in a smaller container/closure system that should be equivalent to the larger container used for storing larger quantities of the API. The smaller container/closure system must have the same composition, closure, and liners and include desiccants if they are also used in the larger container/closure system.

In a short time of 3 months, the accelerated stability studies provide valuable data on the degradation profile of an API and thus assist in validating a particular container/closure system for storage of the API. However, long-term stability studies are essential in developing a retest period and shelf-life for APIs stored in the warehouse under controlled room temperature conditions, which will be defined later in this chapter. A retest period is defined as the period of time during which the API is expected to remain within its specifications. Therefore, it can be used in the manufacture of the corresponding drug product, provided that the API is stored under appropriate environmental conditions. The shelf-life or expiration period for an API is the maximum allowable time period beyond which the API cannot be used in the manufacture of drug products and must be destroyed.

For APIs that exist as solids, a retest period of 1 year is generally supported by long-term stability data and accepted by the pharmaceutical industry. For stable APIs, a shelf-life of 5 years or longer derived from long-term stability and retest data are not uncommon. In the absence of an assigned shelf-life, the API can be retested again after 1 year and assigned a second retest date. This process of retesting can

continue as long as the degradation levels and other quality attributes remain well within specifications. Stability studies to justify assigned retest and expiration dates should be repeated by the drug product manufacturer if the API is repackaged in a different container than that used by the API manufacturer.

Packaging

The FDA guidance [14] entitled "Container Closure Systems for Packaging Human Drugs and Biologics" includes information on container/closure systems for packaging of APIs. In general, APIs are solids; for such APIs, the container/closure system for storage or shipment of APIs usually consists of a fiber drum containing double low-density polyethylene liners that are closed with twist ties. For protection from moisture and thus to assure stability, a desiccant may be placed between the bags if necessary. In that event, the stability samples should also contain appropriately placed desiccants to simulate the configuration of the larger container/closure system.

Shipment

API manufacturers should evaluate test results for critical test attributes such as assay and degradants when they are near specification limits before shipment of batches to drug product manufacturers. Existing stability data should be studied to ensure that such batches will remain within specifications, allowing for analytical measurement errors when initially tested at the API manufacturer's site and also at the assigned retest or expiration dates. If stability data are not available for a batch with test results approaching the specification limits, the particular API batch representing the worst case for its closeness to the specification limits should be studied under long-term stability conditions to develop the stability profile to justify quality-control release and shipment of such batches.

Because the vast majority of APIs are imported from foreign countries, Customs and the FDA require verification of the integrity of the container/closure system's labeling information and the manufacturer's analytical documentation to rule out pilferage or tampering. If the container was opened during transit and the API was exposed to the atmosphere, even for a brief duration, the stability profile of the API could be affected and the possibility of contamination could arise. Therefore, at the minimum, assay, impurities, and degradant profile of the API should be determined at the finished product manufacturer's site. The results should be compared with the API manufacturer's certificate of analysis to verify that the quality of the API has not been compromised.

INTERMEDIATES FOR DRUG PRODUCTS

In general, the manufacturing process for both immediate-release (IR) and modified-release (MR) solid oral dosage forms begins with the mixing of the required APIs and excipients, then proceeds through stages of intermediates, and finally ends with the production of finished products, such as capsules and tablets. These intermediates are known as blends, intermediate pellets, cores, etc.

Specifications

Separate specifications are required to verify the quality of the intermediates used in the production of the finished product. Usually, the analytical methods for the finished product are also utilized in testing of intermediates.

Holding Time

21CFR Part 211.111 requires, where appropriate, time limits for the completion of each phase of production to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation must be justified and documented.

A draft guidance [5], though subsequently withdrawn by the FDA, represented the agency's approach at the time in favor of an intermediate to be held for a maximum period of 30 days from the date of production without being retested before its use in manufacturing. A holding time period of 1 month, instead of 30 days, would also be acceptable, if that is necessary for scheduling convenience. In the guidance, the date of production is defined as the initial date that an API has been added to the inactive ingredients during manufacturing. An intermediate that is held longer than 30 days (or 1 month) should be retested before use. The first production batch of the corresponding finished product should be monitored through long-term stability studies. For blends, the purpose of retesting is to ensure that they have remained stable and that no degradation or demixing took place during prolonged storage. For intermediate pellets, retesting ensures that the dissolution quality has not been affected. Retesting of cores assures that the assay, degradation, and dissolution results are acceptable.

If a longer holding time, for example, 3 months, is necessary to facilitate routine production planning, the quality of an intermediate batch stored in the warehouse under the controlled room temperature condition should be checked for the duration of the holding time. The guidance suggests that at least three test points beyond the initial release should be selected for stability testing. The first finished product batch produced from an intermediate held for the desired duration in the warehouse should be tested. If the test results are found to be satisfactory upon completion of the stability testing of the finished product batch, the holding time of 3 months is deemed to have been qualified and can be routinely used without further stability testing of future batches of the intermediate and the corresponding IR or MR drug products if these intermediate batches are held for not more than 3 months. Because the expiration date of the finished product is assigned from the date of production as defined above, its shelf-life is essentially shortened by the length of a holding time greater than 30 days (or 1 month). Therefore, it is advisable to limit the qualification of the holding time to 3 months or shorter. It should be noted that, if an intermediate is not stable for 30 days (or 1 month), its holding time should be appropriately decreased after review of its short-term stability profile.

DRUG PRODUCT STABILITY

Stability testing plays a crucial role in the development of generic drug products. It provides valuable information regarding the behavior of drugs when exposed to

temperature, humidity, and light. For solid oral generic dosage forms usually packaged in high-density polyethylene bottles, photostability is not generally considered to be an important contributor to degradation and thus will not be discussed further in this article. The FDA regulations governing drug product stability are stated in 21CFR 211.166, which require a written testing program to assess the stability characteristics of drug products. The FDA has published a guidance [4] to harmonize the design and execution of stability testing programs. In addition, ICH guidances [6,15] on stability testing of new drugs are available. Published literature [16] provides further information on designing stability testing programs.

Pharmacopeial and Nonpharmacopeial Products

With the aim of harmonizing the quality standards for generic drugs, USP has provided many monographs for testing of such drugs. However, with the patent expirations of an increasing number of branded drugs, the corresponding monographs may not be available in the USP, its supplements, subsequent editions or Pharmacopeial Forum (PF) for public review, before formulation development, ANDA submission, and marketing of generic drugs. Because monographs for these products need to be independently developed by the generic manufacturers, additional development and validation resources should be allocated to meet the twin goals of FDA approval and market launch in a timely manner.

Specifications and Test Methods

ANDAs require inclusion of appropriate and scientifically justifiable specifications and validated test methods for generic products. The CGMP regulations require that each drug product meets the approved specifications when tested by the approved stability-indicating methods. ANDAs also require inclusion of stability specifications for test attributes such as assay, degradants, and dissolution rates. The test results of long-term and accelerated stability samples of each drug product must conform to its stability specifications at least until the approved shelf-life of the product.

For drug products listed in the USP, the pharmacopeial specifications and test methods should be followed. Often, the older pharmacopeial monographs do not include limits for degradants. For such products, the published FDA guidance (17) on the subject of setting specifications for degradants should be followed.

For nonpharmacopeial drug products, the USP, which contains numerous monographs and guidelines titled as general chapters, is a valuable resource in setting templates for specification and testing methodology. The ICH Q6A guidance (18) should also be used as a general guide for ANDA submissions. Quality-control and stability results as well as expected manufacturing and analytical variables should be evaluated when setting stability specifications. Valid statistical approaches may be utilized. Data generated from testing of the brand company's reference listed drug product in the FDA publication entitled "Approved Drug Products With Therapeutic Equivalence Evaluations," commonly known as "The Orange Book," can also be used to support the specifications proposed in an ANDA application. As a valuable aid in the development of analytical methods for noncompendial drug products, any

information that is globally available from published articles in scientific journals and/or in international pharmacopoeias should be utilized.

In all cases, whether pharmacopeial or nonpharmacopeial analytical procedures, it must be demonstrated that the API and any associated impurities from the synthesis of the API as well as excipients are all separated from the degradation products of the API present in the matrix of the drug product. This is achieved through method validation, which is discussed below.

Method Validation

Stability data serve as a barometer for the shelf-lives of drug products. Stable products are produced from validated production processes that are expected to be in a state of statistical control from one batch to another. It is therefore imperative that every effort be made to ensure that the analytical procedures for measurement of critical stability parameters are fully validated. HPLC has become a universal tool for stability testing because of its demonstrated capability of resolving the main component from degradants and any associated synthesis impurities. The stability-indicating capability of a particular HPLC method is governed by its degree of separation, which is established by conducting forced degradation studies of drugs under various stressed conditions of temperature, humidity, oxygen, acid, base, UV light, and visible light. The details of the development of stability-indicating analytical procedures are included in a separate chapter in this book (Chapter 3) and also in several published guidelines [9–13].

An important component of an ANDA application consists of completed analytical method validation reports. During or after approval of an ANDA application, the FDA usually requests samples and test data to conduct regulatory validation. To fulfill this request, the applicant should follow the published FDA guidance on this topic [19]. In performing the tests, the FDA laboratories will apply the regulatory methods, which are the analytical methods provided in the ANDA application.

For drugs with published monographs in the current USP, the analytical methods are those legally recognized under Section 501(b) of the Federal Food, Drug, and Cosmetic Act. In this respect, 21 CFR Part 211.194(a) (2) states that the analytical methods described in the USP do not require complete validation. The regulation, however, requires that the suitability of all testing methods must be verified under actual conditions of use. In other words, the pharmacopeial methods should be validated to establish their suitability for specific drug products manufactured by generic companies. This is understandable because stability data are critical attributes of drug products. An important advantage will be gained by conducting method validation consistently for all pharmacopeial and nonpharmacopeial products in raising a company's analytical standard in the eyes of FDA reviewers of ANDA applications as well as FDA investigators during on-site compliance inspections.

FDA and ICH Guidelines

In 1994, the Center for Drug Evaluation and Research (CDER) of the FDA accepted the ICH stability testing conditions [6] for new drugs. In a letter to all ANDA

applicants, the Office of Generic Drugs (OGD) of CDER stated that its accelerated stability condition, 40 ± 2°C, 75 ± 5% RH, in support of controlled room temperature tentative expiration dating for ANDA products, was identical to the ICH conditions and would remain unchanged for ANDA submissions [20].

In 1995, the OGD issued a position paper on the conditions required for long-term stability testing of generic drugs, which was posted on the FDA website [20]. The long-term stability testing is required to validate the tentative expiration dating derived from accelerated stability studies. The OGD stated that the ICH recommendations of 25 ± 2°C and 60 ± 5% RH, would be acceptable for long-term stability testing for ANDA applications. Alternatively, the OGD would also continue to accept long-term stability data conducted at the previously allowable conditions of 25°C to 30°C and at ambient humidity. Although both sets of conditions have continued to be allowed by the OGD in ANDA submissions, the international generic community has clearly progressed toward harmonization with the ICH conditions.

Stability Protocol

The stability protocol should be carefully developed by the quality-control unit responsible for conducting and monitoring stability studies. The protocol should consist of the stability study design factors, such as package sizes, sampling time points, strengths, bracketing, and matrixing. It should specify the environmental conditions for accelerated and long-term stability of packaged products and for bulk stability of unpackaged products. It should also include validated stability-indicating analytical procedures and stability specifications. The protocol must be included in an ANDA submission for approval by the OGD. Subsequently, if any changes are made to the protocol, the revised protocol must also be submitted for approval again by the OGD.

The following lists some key points of a stability protocol for a long-term stability testing program of a solid oral dosage form consisting of one strength and packaged in multiple sizes:

- The first three production lots will be packaged for stability testing.
- A bracketing design will be employed because the container/closure systems of the multiple sizes are chemically equivalent.
- The smallest and largest package sizes only will be stationed in the long-term stability chamber under the ICH storage conditions of 25 ± 2°C and 60 ± 5% RH.
- At least one production batch will be packaged in the smallest and largest package sizes and added annually to the long-term stability testing program.
- Testing will be conducted at 0, 3, 6, 9, 12, 18, and 24 months and annually after 24 months until the expiration date has been reached or longer to evaluate the possibility of extending the current expiration period.
- Stability testing criteria will include appearance, assay, loss on drying, known and unknown degradation products, and dissolution.
- Stability data will be evaluated to justify expiration dating and statistical analysis may be employed if required.

- Stability data will be included in the annual report (AR) submission to the OGD.
- Any batch with nonconforming stability data will be recalled from the market with the required notification to the FDA.

Shelf-Life Development

Shelf-life is the time period during which a drug product is expected to remain within its specifications, provided that it is stored under the conditions defined on the container label. An expiration or expiry date is the date on the container label of a drug product, designating the time period before the end of which a batch is expected to remain within the approved shelf-life specification, if stored under the labeled conditions, and after which it must not be used. Regulation 21 CFR Part 211.137 requires that a drug product must bear an expiration date determined by appropriate stability testing in accordance with 21 CFR Part 211.166. The expiration dates must be related to the storage conditions stated on the labeling as determined by the stability studies conducted as described in 21 CFR Part 211.166. If the drug product is to be reconstituted at the time of dispensing, its labeling must bear expiration date information for both the reconstituted and unreconstituted drug products. It should be noted that 21 CFR Part 201.17 requires that the expiration dates must appear on the container labeling.

21 CFR Part 211.166(a) specifies that the results of stability testing must be used in determining appropriate storage conditions and expiration dates. 21 CFR Part 211.166(b) requires testing of an adequate number of batches of each drug product to determine an appropriate expiration date. The regulations allow use of accelerated stability studies to support a tentative expiration date if full shelf-life stability studies are not available at the time of ANDA approval. Where data from accelerated stability studies are used to project a tentative expiration dating period that is beyond a period supported by actual shelf-life studies, long-term stability studies must be conducted, including drug product testing at appropriate intervals until the tentative expiration dating period is verified or the appropriate period is determined. In general, the use of an overage of an API to compensate for degradation during the manufacturing process or a product's shelf-life, or to extend the expiration dating period, is not acceptable [7]. Additional information on the subject of shelf-life development has been published [16,21].

Stability data should be developed for the drug product in each type of container/closure system proposed for marketing or bulk storage. Bracketing and matrixing designs, which will be discussed separately in this chapter, may be used if included in the approved stability protocol.

Action Limits

Long-term stability testing is conducted to assure that the drug product will be within its shelf-life specifications during the expiration period. Action limits tighter than the specification limits should be set to assure that any batch with

initial test results close to the action limits is evaluated through an appropriate course of action. By definition, action limits are the maximum or minimum values of a test result that can be considered to be the boundaries of acceptability without requiring further actions. Results less than the minimum or greater than the maximum action limit indicate that an action must be taken. For example, if an assay or degradant or dissolution result is near but outside the action limits, an appropriate action would be to monitor this batch by long-term stability testing to assess whether the batch will meet the shelf-life specifications. Conforming stability results for this batch also builds up a database in the sense that a future batch with a similar result need not be subjected to stability. That is, a worse-case approach can be taken in deciding whether a future batch would require long-term stability testing. From among all of the batches of the product on long-term stability, the worse-case batch, which must still conform to specifications, is defined as that batch with results that are outside and farthest from the action limits. If the test results of a future batch are outside the action limits but are superior to the results of the worse-case batch, this batch should not require long-term stability studies. However, if the test results pass but are marginal with respect to the shelf-life specifications with no allowance for analytical variability, that batch should be rejected to avoid the risk of a stability failure and consequent recall. It should be noted that anytime an atypical batch is produced, a separate manufacturing investigation should be conducted to determine and correct the root causes for the production problem.

Expiration Date Assignment

The computation of the expiration dating period of a drug product batch should begin not later than the date of the quality-control release of that batch and the date of release should not exceed 30 days or 1 month from the date of production regardless of the packaging date. If the quality-control release date of the batch exceeds 30 days or 1 month from the date of production, the expiration date should be calculated from 30 days or 1 month after the date of production. The date of production of a batch is defined as the first date that an API was added to the excipients during manufacturing.

The data generated in support of the assigned expiration dating period should be obtained from stability studies conducted under the long-term stability condition consistent with the storage environment recommended in the labeling. If the expiration date includes only a month and year, the product should meet specifications through the last day of that month.

A stability protocol should also include the statistical methods for analysis of stability data in addition to the design of the stability study. The draft guidance [5] on stability testing contains acceptable statistical approaches for the analysis of stability data and for deriving an expiration dating period. Generally, an expiration dating period should be determined based on statistical analysis of long-term stability data.

If the reworking of a drug product is approved in an application, the expiration dating period of a reprocessed batch should not exceed that of the parent batch and the expiration date should be calculated from the original date of production [7].

Annual Stability

After the expiration dating has been verified with three production batches, an ongoing stability testing program for an approved drug product should be implemented in accordance with the postapproval stability testing protocol in the ANDA application. The protocol should include the commitment to place at least one batch of every strength in every container/closure system, such as bottles or blisters, in the annual stability program for the subsequent years. If the manufacturing interval for a drug product is greater than 1 year, a batch of drug product released next year should be added to the stability program. Approved bracketing and matrixing designs should be implemented to reduce the stability testing workload.

Intermediate testing time points may be reduced for annual batches on a case-by-case basis through a prior approval supplement (PAS) [5]. The proposed reduction must be justified based on a history of satisfactory long-term stability data. The reduced testing stability protocol should include a minimum of four time points, including the initial and expiration time points and two time points in between. For example, for an expiration dating period of 36 months or longer, batches should be tested annually. It should be noted that the reduced testing protocol applies only to annual batches and does not apply to batches used to support a postapproval change that requires long-term stability testing at all time points. However, bracketing and matrixing designs may be included in the PAS, which will optimize testing efficiency.

Extension of Expiration Dating Period

An extension of the expiration dating period based on full long-term stability data obtained on at least three production batches in accordance with a protocol approved in the ANDA application may be implemented immediately and does not require prior FDA approval. 21 CFR Part 314.70(d) (5) allows implementation of the extended expiration dating through an AR submission only if the criteria set forth in the approved stability protocol were met in obtaining and analyzing stability data.

Bulk Holding

Upon completion of manufacturing, the finished products, such as capsules and tablets for solid oral dosage forms, are usually held for a period of time, often called the bulk holding time, before packaging. The length of the bulk holding time is usually governed by scheduling of packaging operations and inventory requirements. In the interest of saving development time during routine production, it is advisable to establish the bulk holding time by monitoring the controlled room temperature stability of a sample of the ANDA submission batch, which is stored in a smaller container equivalent in composition to the larger container used for storage of unpackaged bulk finished tablets. For example, to simulate the larger cardboard containers used for storage in the warehouse, suggested dimensions of the smaller containers would be $4'' \times 4'' \times 4''$ cardboard containers, double lined with low-density polyethylene bags that are closed with twist ties. The stability study of samples stationed in the warehouse, maintained at the controlled room temperature condition,

should be conducted for the duration of the desired bulk holding time. Typically, this should be not more than 6 months from the date of its quality-control release if this date does not exceed 1 month beyond the date that the API was first used in the manufacturing process. For a holding time of 6 months, testing time points of 0, 3, and 6 months would be adequate unless dictated otherwise by data. For each product strength, the bulk holding time should be established. The established bulk holding time of one strength would not be transferable to the other strengths of a product line without supportive stability data for these strengths. If the bulk holding time is not established concomitantly with the development of the stability profile of the ANDA batch, it will be necessary to establish the bulk holding time post-ANDA approval. This may create some bottlenecks during prospective validation studies in preparation for a product's launch into the market. Generally, if a bulk holding time of not more than 3 months is desired, stability testing beyond the initial quality release testing is not necessary to accept this time frame routinely as a packaging deadline for solid oral dosage forms.

Bracketing

The CDER has accepted the ICH recommendations on bracketing designs for stability studies, which are available in published guidances [5,22]. In a bracketing design, at any time point for example, only the samples on the extremes of container sizes, fill quantities, and/or dosage strengths are tested. The design assumes that the stability of the samples corresponding to the intermediate conditions is represented by the stability data at the extremes. The guidances that provide extensive details on the principles of various bracketing designs should be studied before the development of a design for a particular product. The general concepts described in the guidances are equally applicable to both new and generic drugs and will be summarized for solid oral dosage forms.

A bracketing design can be used for most types of drug products, including IR and MR solid oral dosage forms where the drug is available in multiple sizes or strengths. For a range of container sizes/fill quantities for a drug product of the same strength, a bracketing design may be applicable if the material and composition of the container and inner seal of the closure are the same throughout the range. Where either the container size or fill quantity varies, whereas the other factors remain the same, the bracketing design may be applicable without justification. Where both container size and fill quantity vary, a bracketing design is applicable if appropriate justification is provided. Such justification should demonstrate that the various aspects (e.g., surface area/volume ratio, dead space/volume ratio, container wall thickness, and closure geometry) of the intermediate sizes will be adequately bracketed by the extremes selected.

For a range of dosage strengths for a drug product in the same container/closure system with identical material and identical size, a bracketing design may be applicable if the formulation is identical or very closely related with respect to the components/composition. Examples of the former include tablet weights from a common blend made with different compression forces or capsule weights made by filling a common blend into different-size capsule shells. A very closely related formulation

means a range of strengths with similar, but not identical, basic composition such that the ratio of the active ingredient to excipients remains relatively constant throughout the range, allowing for addition or deletion of colorant or flavoring, for example. Where the strength and the container size and/or fill quantity of a drug product vary, a bracketing design may be applicable with the necessary justification.

A bracketing design should always include the extremes of the intended commercial sizes and/or strengths. However, if the extremes are not truly the worst-case selections based on strengths, container sizes, and/or fill quantities, use of a bracketing design is not appropriate. Where the amount of the active ingredient changes, whereas the amount of each excipient or the total weight of the dosage unit remains constant, bracketing may not be applicable unless justified.

If the market demands require discontinuing either the lowest or the highest bracket extreme and marketing of the intermediate sizes or fill quantities are still needed, the post-ANDA approval commitment to conduct ongoing stability at the extremes of the bracketing should be maintained.

Before implementing a bracketing design, its effect on shelf-life verification should be assessed. If the stability of the extremes is shown to be different, the intermediate packages should not be assumed to be more stable than the least stable extreme. In other words, the shelf-life of the intermediate packages should not exceed that for the least stable extreme of the bracket.

A bracketing design from the guidance Q1D is illustrated in the following table to demonstrate the concept behind bracketing [22]. This example is based on a product available in three strengths and three container sizes. For the selected combination of batches, the postapproval stability program should require testing at all time points to assure that the results continue to meet all stability-related specifications.

Example of a bracketing design:

		Strength								
		50 mg			75 mg			100 mg		
Batch		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Container size	15 cc	T	T	T				T	T	T
	100 cc									
	500 cc	T	T	T				T	T	T

T = test sample at all time points specified in the post approval commitment.

An intended bracketing design should be included in the stability testing protocol of the ANDA application. If the ANDA application does not contain the bracketing design, a supplemental application and approval will be required before implementation of the design for stability studies of routine production batches.

Matrixing

The CDER has also accepted the ICH guidance on matrixing, which is another type of a reduced design based on different principles [5,22]. In a matrixing design, a fraction

of the total number of samples are tested at any specified time point. At a subsequent time point, different sets of the total number are tested. This design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container/closure systems.

Matrixing results in reduced testing when more than one variable is being evaluated. In the matrixing design, each combination of factors should be tested at the specified time points to obtain a balanced influence of the factors on the variability of the stability results. Whereas the design will be governed by the factors that would be present in the full stability program, all batches should be tested initially and at the final time point.

The guidances [5,22] provide extensive details on matrixing designs and the important concepts outlined in these guidances are summarized below for solid oral dosage forms.

The factors that can be matrixed include batches, strengths with identical formulation, container sizes, fill quantities, and intermediate time points. Factors that should not be matrixed include initial and final time points, test parameters, dosage forms, strengths with different formulations (i.e., different excipients or different active ingredient/excipient ratios), and storage conditions.

The principles behind a matrixing design can be best explained with the following example reproduced from the ICH Q1D guidance [22].

Matrixing time points and factors for a product with three strengths and three container sizes:

	Strength								
	S1			**S2**			**S3**		
	Container size			**Container size**			**Container size**		
	A	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
Batch 1	T1	T2		T2		T1		T1	T2
Batch 2		T3	T1	T3	T1		T1		T3
Batch 3	T3		T2		T2	T3	T2	T3	
Time points (months)	0	3	6	9	12	18	24	36	
T1	T		T	T	T	T	T	T	
T2	T	T		T	T		T	T	
T3	T	T	T		T	T		T	

S1, S2, and S3 are different strengths; A, B, and C are different container sizes; T = sample to be tested.

Generally, the matrixing design is applicable if the supportive stability data exhibit small variability and thus can predict product stability accurately. If the supportive data show large variability, a matrixing design should not be used. If a matrixing design is applicable, the extent of reduction from a full design in the number of samples to be tested depends on the factor combinations selected as shown in

the above tables. The greater the number of factors and greater the number of levels in each factor, the greater is the extent of reduction in the number of samples to be tested. Any reduced design is justifiable only if it has the ability to accurately predict shelf-life.

An intended matrixing design should be included in the stability testing protocol of the ANDA application. Because of the potential complexity of matrixing designs, it is advisable to discuss a design in advance with the OGD before its implementation in the stability program. If the ANDA application does not contain the matrixing design, a supplemental application and approval will be required before implementation of the design.

Controlled Room Temperature

Generally, drug product labeling specifies storage temperature and, in some cases, humidity requirements to maintain product stability. The General Notices section in the USP defines various storage conditions and should be used as a guide to ensure appropriate storage conditions consistent with the product's labeling requirement. The majority of drug products require controlled room temperature storage.

In the USP, the controlled room temperature is defined as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C to 25°C (68°F–77°F), which results in a mean kinetic temperature (MKT) calculated to be not more than 25°C, and that allows for excursions between 15°C and 30°C (59°F and 86°F) that are experienced in warehouses, pharmacies, and hospitals. Provided that the MKT remains in the allowed range, transient spikes up to 40°C are permitted as long as they do not exceed 24 hours. Spikes above 40°C may be permitted if the manufacturer provides data on effects of storage temperature variations. The MKT is a calculated value that may be used as an isothermal storage temperature to simulate the nonisothermal effects of storage temperature variations. The procedure for calculation of the MKT is included in the USP, General Chapter <1151>.

Stability of Products Containing Iron

In 1997, the FDA published the iron regulations requiring label warnings and unit-dose packaging for solid oral drug products that contain 30 mg or more of iron per dosage [23]. The regulations were issued to reduce the likelihood of accidental overdose and serious injury to young children through the use of unit-dose packaging. Such packaging was considered to limit the number of doses a child may ingest if the child gained access to the product.

Appropriate expiration dates for drug products in unit-dose packages were required to meet the iron regulations. Accelerated stability testing was not considered to be applicable to drug products containing iron, especially multivitamin products, because they were known not to perform well under the unrealistic stressed accelerated conditions. Therefore, long-term stability testing was the only method to determine the expiration date. After publication of the iron regulations, which became

effective on July 15, 1997, a grace period of 2 years, expiring on July 15, 1999, was provided to allow manufacturers to package products in unit-dose blisters and continue to market the product with reduced expiration dating as defined in the guidance. At the same time, the manufacturers were required to initiate and conduct long-term stability studies to establish anew the expiration dating for existing products packaged in unit-dose blisters. Notice should be taken that, for new products containing 30 mg or more of iron per unit dose, the product must be packaged in unit-dose blisters and set up on long-term stability to develop expiration dating before market entry.

Reprocessing and Reworking

Reprocessing and reworking were defined in a draft guidance [7], and though the guidance was later withdrawn by the FDA, it represented the agency's attempts to clarify these terminologies. Reprocessing is the introduction of an in-process material or drug product, including the one that does not conform to a standard or specification, back into the process and repeating steps that are part of the approved manufacturing process. Continuation of a process step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing. For most drug products, reprocessing does not require to be described in an ANDA application unless it is known that there is a significant potential for the reprocessing operation to adversely affect the quality attributes of the drug product. Generally, a reprocessed drug product does not require stability testing unless warranted otherwise because of quality concerns.

Reworking is subjecting an in-process material or drug product that does not conform to a standard or specification to one or more processing steps that are different from the manufacturing process described in the ANDA application to obtain acceptable quality in-process material or drug product. In general, reworking operations should be generated postapproval and the ANDA application should be updated through the submission of a PAS, unless reworking operations are anticipated and included at the time of the original ANDA application. Reworking of drug products should be justified by monitoring at least one batch representative of the reworked process under accelerated and/or long-term stability testing [7].

Packaging

Section 505(b)(1)(D) of the Act requires a full description of the facilities and controls used in the packaging of a drug product. Essentially, the Act mandates that the integrity of the container/closure system used in the packaging of a drug product must be maintained during routine packaging operations for marketed products. By definition, the container/closure system means the sum of all packaging components that together protect and contain the drug product. For control of the quality of the container/closure system, the USP has established requirements in the General Chapters <661> Containers and <671> Containers—Permeation. For solid oral dosage forms such as capsules and tablets, the USP requirements essentially relate to moisture permeability, oxygen permeability, and light transmission properties of the container/

closure systems. Ultimately, proof of the suitability of the container/closure system and the packaging process is obtained from shelf-life stability studies.

Shipment

Package sizes and the corresponding container/closure systems intended for marketing must be included in the ANDA application with the necessary accelerated and long-term stability data for approval by the OGD. A container/closure system (i.e., shipping containers) used for the transportation of bulk drug products to contract packaging companies should be described in the application [5]. The container/closure system should be adequate to protect the dosage form, be constructed with materials that are compatible with the product being stored, and be suitable for the intended use. The protective properties of the shipping container are verified by the practice of annual stability studies.

If a container closure/system is specifically intended for the transportation of a large quantity of a drug product to a repackaging company, it is considered to be a market package. Usually, such package sizes are well outside the range of the package sizes used in shelf-life stability testing and are not monitored in the annual stability program. For example, the large container closure/system used for bulk holding of capsules or tablets is not usually supported by shelf-life stability data and thus is not usually included in the application as a package to be marketed. It should be noted that such packages cannot be sold to repackagers.

CONTROLLED DRUGS

The Drug Enforcement Administration is the US agency that is responsible for enforcement of the regulations of the Controlled Substances Act. The regulations that are described in 21 CFR Parts 1300 to 1316 define the controls relating to the manufacture, distribution, and dispensing of controlled substances. The controlled substances have been divided into five different classes or schedules. Controlled substances under Schedules I and II require the greatest degree of security and controls. The substances under Schedules III to Schedule V require lesser degrees of control and security. Examples of drug product classifications are heroin (Schedule I), oxycodone hydrochloride tablets (Schedule II), phendimetrazine tartrate tablets (Schedule III), diazepam tablets (Schedule IV), and diphenoxylate hydrochloride and atropine sulfate tablets (Schedule V). To facilitate the use of abbreviations for the different schedules, 21 CFR Part 1302.03(c) has designated the following symbols: CI or C-I for Schedule I, CII or C-II for Schedule II, CIII or C-III for Schedule III, CIV or C-IV for Schedule IV, and CV or C-V for Schedule V.

Storage Requirements for CI to CV Drugs

The FDA regulations require accelerated and long-term stability testing for all drug products regardless of their classification as controlled substances. For such substances, pharmaceutical companies have employed additional controls to assure

security during short-term and long-term storage of stability samples. As an example, the chamber used for long-term stability studies may allocate space for a locked cage for Schedules I and II drugs, which should be situated within the confines of the larger locked cage for Schedules III to V drugs. The chamber also provides a level of security with its own lock. For Schedules III to V drugs, the larger locked cage situated within the chamber provides a second level of security. For Schedules I and II drugs, the smaller locked cage situated within the larger locked cage provides the highest level of security. In all cases, a limited number of personnel should be authorized to access the chamber and the cages containing the controlled drugs for long-term stability testing. For accelerated stability testing of drugs, a small commercially available chamber is traditionally used for the short-term studies. This chamber should allow limited access and be located in a secure area. It should be noted that the general storage requirements of stability samples are also covered in 21 CFR Parts 1301.75(b) and 1301.75(c), which allow dispersing controlled substances throughout the stock of noncontrolled substances in such a manner as to prevent the theft or diversion of the controlled substances from the stability chamber. Before designing and implementing procedures for securing controlled drugs in the accelerated and long-term stability chambers, it is essential to consult with the Drug Enforcement Administration and seek their approval.

SUBMISSION REQUIREMENTS

Considering that a significant body of stability data is usually available on the branded drugs at the time of their patent expirations and well before an ANDA can be submitted, the ANDA submission requirements for stability data are less extensive than the new drug application (NDA) requirements for such data. Thus, valuable time is saved by the generic industry and also in the regulatory review by the OGD, which contributes to the process of quick introduction of cheaper generic products into the market for the benefit of all patients.

ANDA Submission

General Requirements for ANDA Submissions for Generic Products

Accelerated stability data at 0, 1, 2, and 3 months on a minimum of one batch, which can be a pilot-scale batch with a minimum batch size of 100,000 capsules or tablets, are required [24]. For multiple sizes and strengths, scientifically justifiable bracketing and matrixing designs can be employed. The tentative expiration dating period of up to 24 months may be granted based on satisfactory accelerated stability data unless not supported by the available long-term stability data. Available long-term stability data should be included in the original ANDA application and subsequent amendments.

Additional stability studies (12 months at the intermediate conditions or long-term stability data through the proposed expiration date) are required if “significant change” is seen after 3 months during accelerated stability. The tentative expiration dating will be determined based on available data from the additional study.

Where "significant change" occurs under accelerated testing, additional testing at an intermediate condition, 30 ± 2°C/60 ± 5% RH, should be conducted. "Significant change" at the accelerated condition is defined as follows [5,6]:

- A 5% potency loss from the initial assay value of a batch
- Any specified degradant exceeding its specification limit
- The product exceeding its pH limits
- Dissolution results exceeding the specification limits for 12 capsules or tablets
- Failure to meet specifications for appearance and physical properties, e.g., color, caking, and hardness

Should significant change occur at 40°C/75% RH, the ANDA applications should include a minimum of 6 months' stability data at 30°C/60% RH; the same significant change criteria will then apply. The long-term testing should be continued beyond 12 months to derive shelf-life data.

Postapproval Changes

21 CFR Part 314.70(a) requires applicants to notify the FDA when there are any changes to an approved ANDA application. To facilitate less burdensome post-approval changes within the meaning of this regulation, the FDA has published three guidances [25–27] on postapproval changes, including two separate scale-up and postapproval change (SUPAC) guidances on IR and MR products. These guidances provide recommendations on the following categories of postapproval changes:

- Changes in the components and composition
- Changes in the site of manufacture
- Changes in batch size (scale-up/scale-down)
- Changes in manufacturing equipment and manufacturing process

The guidances have defined levels of changes and, for each level of change, specified the requirements for stability data in support of the change. Because of the increasing necessity for site transfers in the pharmaceutical industry, stability documentation requirements for site changes are discussed below. The stability documentation requirements outlined in SUPAC-IR and SUPAC-MR for the other categories of changes are not included in this discussion.

Site Transfer

Site transfer usually consists of relocating manufacturing, packaging, and/or laboratory testing operations to a different site or to an alternate site. With increasing competition and consolidation in the generic pharmaceutical industry, site transfer of products has become popular to increase operational flexibility and speed and, at the same time, decrease cost of marketing products.

To facilitate the site transfer process, the FDA has published guidances [25–27] on the requirements for postapproval site transfer of products from the originally approved location to a different location.

In this section, the stability testing requirements and submission categories for the three levels of site transfer of solid oral dosage forms defined in SUPAC-IR and SUPAC-MR are summarized. For detailed information on the chemistry documentation, dissolution, bioequivalence, stability, and reporting requirements, the above-noted guidances should be studied.

An IR solid oral drug product is defined as a product that allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug. An MR drug product is defined as a product whose drug content is released as a function of predetermined time points. MR solid oral dosage forms include both delayed and extended release drug products.

Level 1: Level 1 changes are defined as site changes within a single facility where the same equipment, standard operating procedures (SOPs), environmental conditions and controls of temperature and humidity, and personnel common to both manufacturing sites are used and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

The Level 1 site change requires an AR submission. No additional accelerated or additional long-term stability data from the different location are required.

Level 2: Level 2 changes are defined as site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOPs, environmental conditions and controls of temperature and humidity, and personnel common to both manufacturing sites are used and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

The Level 2 site change requires a changes being effected (CBE) supplement. For IR products, no accelerated stability data are required in the CBE submission. The first production batch produced at the different site should be monitored under long-term stability and the data should be submitted in an AR. For MR products, one batch with 3 months' accelerated stability data should be included in a CBE supplement and long-term stability data of the first production batch should be reported in an AR.

It should be noted that if the different site does not have a satisfactory cGMP inspection for the type of products being transferred, a PAS should be submitted instead of a CBE submission.

Level 3: Level 3 changes consist of a change in the manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, the same equipment, SOPs, and environmental conditions and controls should be used in the manufacturing process at the new site and no changes should be made to the manufacturing batch records except for administrative information, location, and language translation, where needed.

In the SUPAC guidances, a significant body of information on the stability is defined as that which is likely to exist after 5 years of commercial experience for new molecular entities or 3 years of commercial experience for new drugs. The scenario

that provides for the following simpler submission requirements is applicable to generic drugs that are marketed after 20 or more years following initial marketing of the corresponding branded drugs.

For Level 3 site transfer of generic IR drugs, 3 months' accelerated stability data from one batch should be included in the CBE supplement and long-term stability data from the first production batch should be included in ARs.

For MR products, the Level 3 change requires a PAS. For site transfer of generic MR drugs, 3 months' accelerated stability data on one batch should be included in the PAS and long-term stability data of the first three production batches should be included in ARs.

COMPLIANCE ISSUES

Regulatory implications governing stability testing need to be clearly understood and communicated throughout an organization to assure compliance with regulations and guidances. It should not be forgotten that contract testing laboratories and drug substance manufacturers constitute an extension of the organization with respect to the need for prompt communication and compliance with regulations.

Drug Substance (API) Stability

Stability testing of the generic drug substance (API) is conducted by the API manufacturer following a protocol included in a DMF submission. Usually, the DMF is referenced in the ANDA application submitted by drug product manufacturers and its review is triggered by the submission of the ANDA. The DMF needs to be updated with new annual stability data as they become available. If accelerated stability testing was conducted to justify process change(s), such information should be provided via amendment of the DMF in a timely manner. Failure to update the DMF may adversely affect the compliance status of the drug substance as well as the corresponding drug product especially in the event of unreported significant process changes and unavailability of stability data. Significant changes in the manufacturing process and/or equipment and/or site of manufacture for a drug substance may require separate stability evaluation and supplemental submissions to the FDA in ARs, CBEs, or PASs. Therefore, it is imperative that the drug substance manufacturers keep the drug product manufacturers in the loop to ensure timely supplemental submissions on drug products. Theoretically, in the absence of timely submissions on significant process changes, the drug substances and drug products may both be considered to be out of compliance with the FDA regulations.

Drug Product Stability

Stability testing of the generic drug substance (API) is conducted by the API manufacturer following a protocol included in an approved ANDA application. The protocol specifies time points for "pulling" stability samples for analysis. A log of "pull" dates for all stability samples should be maintained. It may be advantageous to

initiate testing by performing the assay first and recording this date as the appropriate time point in the stability records and reports. It is important to complete testing of the samples in a timely manner. Delays in completion of testing should not exceed 30 days or 1 month from the dates when samples were collected from the stability chamber. Every attempt should be made to avoid omission of testing time points. Missing time points in stability reports have been cited by FDA investigators on the Notice of Inspectional Observations, FDA Form 483.

CGMP Considerations

21 CFR Part 211.166 requires a written testing program to assess the stability characteristics of drug products. To comply with this requirement, SOPs should be written to define the details of the stability program, such as container sizes/fill quantities, testing time points, temperature, and humidity conditions for the accelerated and long-term stability chambers.

The chambers used for accelerated and long-term stability studies should be validated. A validation protocol describing the requirements for installation qualification, operational qualification, and performance qualification should be prepared and executed. The installation qualification essentially verifies that the chamber was properly installed as specified by its manufacturer and provides controlled access to selected personnel only. The operation qualification should verify conformance of the chamber's performance to specifications for temperature, humidity, airflow, and water pressure. The performance qualification study should be conducted over several days to ensure long-term reliability of the chamber. Temperature and humidity mapping studies should be incorporated in the performance qualification to ensure that temperature and humidity gradients are acceptable. The completed validation report should be approved by the Quality Assurance (QA) Department. Upon approval of the validation report, the chamber can be used for stability studies. For continued quality assurance, temperature and humidity data for both accelerated and long-term stability chambers must be recorded continuously and these records must be archived for future audits by the QA personnel and FDA investigators.

FDA Inspection

Stability testing methodology and data constitute an integral part of an ANDA application on a specific product and provide the foundation for continued demonstration of the validity of the expiration dates of all products manufactured. This information is subject to inspections by FDA investigators, usually from a local district office. The FDA evaluates the integrity of stability data during preapproval inspections related to one or more ANDA applications and during CGMP inspections to assess the company's compliance with regulations. During these inspections, the method validation reports in support of the stability-indicating analytical procedures, stability data, and the temperature and humidity records for the accelerated and long-term stability chambers must survive the close scrutiny of the investigators to succeed in the process of obtaining FDA approval of the ANDA applications and maintaining

the facility's CGMP status. Examples of typical issues that may delay FDA approval of applications and adversely affect acceptable CGMP status are as follows:

- Inadequate resolution of impurities and degradants from the main peak in the HPLC analysis
- Inability to detect and accurately quantify small impurities in the 0.1% range
- Unsatisfactory investigations of out of specification (OOS) stability data
- Failure to follow stability testing procedures submitted in the application
- Inadequate method validation
- Inadequacy of the SOPs for stability testing
- Omission of testing time points
- Missing temperature and humidity charts for the stability chambers
- Lack of periodic calibration of the chambers

Documentation

21 CFR Part 211.180, which contains regulations on general requirements for records and reports, requires that all records must be retained for at least 1 year after the expiration date of the batch. The regulations require that all records must be readily available for FDA inspections during the retention period at the establishment where the activities described in such records occurred. It is important to interpret this regulation correctly for retention of stability data. It is essential that the original accelerated and long-term stability data in support of the shelf-life of a product are maintained indefinitely because such data provided the foundation for the established expiration date assigned to all lots of the product. For a product, the particular lot introduced into the ongoing annual stability testing program also represents the continued validity of the expiration dates assigned to all lots of the product manufactured in that year. Therefore, annual stability data for a given year should be retained for at least 1 year past the expiration date of the last lot manufactured in that year. Complete records must be maintained of all stability testing performed as required by 21 CFR Part 211.194(e).

Training

21 CFR Part 211.25 on personnel qualifications is also applicable to personnel engaged in stability testing. The regulation requires that each person shall have education, training, and experience, or an appropriate combination thereof, to enable that person to perform the assigned functions. In addition to hiring personnel with the necessary academic background and skills, it is important to certify the newly hired personnel in the analytical procedures employed by the company. The certification process should be formalized in an SOP and should be based on having the new employee and an experienced person conduct the same critical tests, such as assay, impurities, and dissolution on selected lots of the product. The results obtained by the new and experienced employees should be compared. If the new employee's results are unsatisfactory, the certification process should be repeated until satisfactory results are

obtained. In the case of demonstrated poor analytical understanding and accuracy, the employee should not be assigned analytical testing duties.

It is important from the CGMP perspective as well as for laboratory efficiency that training on analytical procedures, laboratory SOPs, applicable CGMP regulations for laboratory operations and record-keeping requirements, and new analytical technology should be a periodic process and formalized in an SOP on training. Trainers should not be limited to laboratory experts only. Instrument manufacturers, technical seminars, and scientific meetings are valuable external training resources, which should be sought, when necessary, in enhancing employees' analytical expertise especially on new technology such as computerized and networked HPLC and gas chromatography systems, multiwavelength photodiode array detection in HPLC analysis, particle size measurement based on laser diffraction, and Fourier transform infrared spectrometry. For training on USP monographs and general chapters and dissolution technology, USP experts provide both off-site and on-site training. Essentially, periodic training demonstrates a company's commitment to continuing improvements in laboratory quality. All certification and training records on all employees should be maintained by the QA Department and presented on request to FDA investigators.

OOS Investigation

The procedure for investigation of out-of-specification (OOS) test results varies within the pharmaceutical industry. With the objective of developing a harmonized approach for investigation of OOS test results, the FDA published a guidance in October, 2006 [28]. The term, OOS results, includes all suspect results that fall outside the specifications submitted in ANDA applications. For products with monographs in the USP, the ANDA specifications would usually correspond to the USP specifications.

The guidance presents the FDA's current policy on evaluation of OOS results and should be viewed as an important resource in evaluating and validating or invalidating OOS stability data. To meet the FDA's requirement, an investigation should be conducted whenever an OOS stability test result is obtained. The guidance requires that the investigation should be thorough, timely, unbiased, well documented, and scientifically defensible. Because the particular annual stability batch with an OOS result represents all batches of the product manufactured in a given year, it is necessary to evaluate all batches manufactured in the year to determine whether or not the OOS result was limited to this batch only. If only one batch is affected by the OOS result and other batches are not, the investigation must show the unique circumstances responsible for the failure of the particular batch to meet specifications and, at the same time, demonstrate clearly that the annual stability program was not compromised.

Annual Product Review

Annual product reviews are mandated in 21 CFR Part 211.180(e), which states that written records must be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. As an important

objective of the annual product review program, the results of ongoing annual stability batches must be reviewed for continued justification of the shelf-lives of all products manufactured. If stability results cast any doubt with respect to the validity of the shelf-life of a particular product, the situation should be investigated in a timely manner to determine the assignable reasons for the stability problem. If warranted by the investigation, the shelf-life should be reduced until the problems, for example, marginally acceptable assay results with respect to specifications, have been identified and addressed.

Field Complaint

21 CFR Part 211.180(e) (2) requires a review of field complaints and investigations conducted for each drug product. The complaints may provide clues to the product's performance in the field and should be studied to show whether they relate to any physical or chemical changes in the product's specifications. Such changes can be caused by contamination in the plant or the field or can be caused by the packaged product's physical and chemical stability characteristics. For example, chemical discoloration of capsules or tablets due to moisture, caking of tablets, or ineffective product may indicate compromised integrity of the particular lot of the container/closure system and/or the need to tighten up on batch manufacturing parameters.

Recall

The failure of any annual stability batch to meet any specification needs to be promptly and thoroughly investigated to ascertain the reason(s) for the OOS result and to ascertain whether other batches that were not included in the annual stability program are affected. Examples of failures during annual stability would be nonconforming assay, degradant, or dissolution results. The unacceptable batches identified in the investigation should be withdrawn from the market. The FDA should be informed and a prompt voluntary recall of all affected batches should be conducted with the consent of the FDA. This will avoid possible product seizures by FDA and/or court injunctions. In addition, 21 CFR Part 314.81(b) (1) requires submission of a Field Alert Report to the local FDA district office within 3 working days of the occurrence of the OOS result.

STABILITY SOFTWARE

For over a decade, it has been a common practice by the drug manufacturers to rely on stability software to store, organize, retrieve, and analyze the vast amount of stability data generated by laboratory testing. Stability software may either be developed in-house or procured from vendors.

Computer Validation

The stability software must be validated according to the commonly accepted principles of computer software validation. If the stability software is developed in-house, it is important that internal experts are available for validation. If it is decided to outsource validation, the process will be costly because external experts will have

to fully understand the software to develop and execute an appropriate validation protocol. Stability software supplied by vendors is usually accompanied by a validation package for on-site execution. Regardless of whether validation is conducted by internal or external validation specialists, the QA Department's approval will be required before use of the software. To facilitate the approval process, QA personnel will require computer software validation training, whether provided by vendors or through various computer validation seminars, to develop the necessary expertise to assess the validation report before sign-off.

21 CFR Part 11

21 CFR Part 11 (commonly referred to as "Part 11") states the regulatory requirements for electronic records and electronic signatures. In the regulation, electronic records are defined as records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted electronically. The regulations also define electronic signatures that can be used instead of manual signatures and require complex controls to assure the security and integrity of electronic signatures. By definition, all stability software and stability data maintained and processed by the software are electronic records. In many companies, manual signatures may still be employed, which will obviate the need to adhere to the additional and complex requirements for electronic signatures. To clarify the requirements for complying with Part 11, the FDA initially published a guidance that was subsequently withdrawn because of objections from the industry. To facilitate the process of compliance for electronic records and electronic signatures, the FDA developed a simpler guidance which was published in August 2003 [29]. It is important for stability testing laboratories to understand and utilize the guidance for compliance with Part 11.

VALUE OF STABILITY

Long-term stability studies assure, on an ongoing basis, that the products continue to conform to quality control specifications and thus maintain their safety and efficacy requirements throughout their shelf-lives. The studies consistently build up a long-term track record of stability data. Stable results continue to demonstrate that raw materials, manufacturing processes, packaging components, and packaging processes have all been in a state of control and have resulted in stable products until at least their expiration periods. The ongoing stability studies also serve as an invaluable tool in the quality-control system to detect any unexpected spikes in the test result(s) during the shelf-life of a product and allow for implementation of corrective actions after investigating and ascertaining the root causes of the problem.

COST OF STABILITY

Annual stability studies assure that production processes continue to be in a state of control to produce stable drug products. Regulations require that, for each marketed product, one lot produced per year must be set up on long-term stability studies for at least the duration of the expiration period of the product. Thus, for a given number of

marketed products, the cost of ongoing stability studies is independent of the number of batches produced in a given year. If only one batch is produced in a given year, that batch still must go on annual stability. If 100 batches are produced for a certain product, only one batch needs to be set up for stability testing. Clearly, the cost of stability is proportionately greater for low volume products. There is no regulation requiring that the first lot produced in a particular year needs to be on stability. Because the stability workload can be substantial, it is important to spread the workload throughout the year to prevent overloading the first few months of a year with stability testing. This will also spread the cost of stability testing evenly throughout the year.

With the growth of the generic industry, the stability testing workload and thus its cost are destined to grow as well. Ultimately, the cost is borne by the consumers (i.e., patients). Creativity will be required to control the cost of stability. Usually, the stability protocol requires testing at 0, 3, 6, 9, 12, and 18 months and yearly thereafter until the expiry period. For stable products with a documented history of at least 5 years, the stability workload can be reduced significantly through deletion of the intermediate short-term test points of 3, 6, 9, and 18 months. For products with multiple strengths and package sizes, the stability protocol should be amended to reduce testing requirements via justifiable reduction of intermediate time points and appropriate bracketing and matrixing designs. Of course, the amended protocol needs to be submitted to the FDA as a PAS. Upon approval, the reduced time points can be immediately implemented, which will reduce the cost of stability testing and also bring down the price of generic drugs. To further control costs, the stability samples for a given product should be set up in a manner to allow batch processing for laboratory testing.

CONCLUSIONS

Patients depend on high quality and affordable generic drugs that are safe and efficacious. The generic drug industry must make every attempt to lower the cost of drugs without compromising their quality, safety, or efficacy. Raw material, research and development, production, quality control and stability testing, storage, and distribution costs all contribute to the cost of medicines. To control these costs on an ongoing basis, which include the significant costs of stability testing, and concomitantly maintain compliance, creativity will be required to keep up with the evolving regulatory requirements and guidances, competitive industrial practices, technological developments, and changing market demands.

It is common knowledge that brand companies, faced with an ever increasing prospect of many drugs losing their patent protection, have been resorting to court actions to gain one or more 30-month stays of FDA approvals for many generic drug products. Often, just before patent expirations, these companies have employed the tactic of filing pediatric clinical studies to gain an additional 6 months' patent extension, which has effectively blocked FDA approvals of generic equivalents during this period. Meanwhile, the generic industry continues to bear the cost of product development and ongoing stability testing during the exclusivity periods, which ultimately increases the cost of sale.

On the generic side, there is an ongoing battle to obtain the coveted 180-day exclusivity granted by FDA to the first-to-file company of a generic drug product. Also, because of increasing competition among generic manufacturers for market share, monopolistic tendencies have been developing through mergers and locking-in raw material sources through acquisitions or special contracts. A generic company awarded marketing exclusivity by the FDA for a product can market this drug without competition from the other generic companies for 6 months after its patent expiration. As a result, other generic companies cannot recover their development, stability testing, and other costs during this period. These factors are also conducive to increasing the price of generic drugs.

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7 Quality Control and Quality Assurance

Loren Gelber

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INTRODUCTION

In August 1989, the U.S. Food and Drug Administration (FDA) made it clear to members of the generic drug industry that many aspects of current good manufacturing practices (cGMPs) apply to the product development process. The unfortunate problems uncovered at that time led agency investigators to request, for the first time, records showing how formulations were developed. Disappointingly, many firms had little documentation related to product development activities.

In the past, the process of formulation development has often had an almost mystical quality. We have seen a formulator listen to the sound of a listed reference tablet breaking, watch its behavior in 5 mL water, close his eyes, commune with the laws of the universe, and then write down a formulation and manufacturing process. At times, he was so confident that the firm proceeded to produce the abbreviated new drug application (ANDA) batch directly thereafter. Such ex nihilo batches passed the FDA bioequivalence requirements more frequently than one would expect.

Unfortunately, the product development process described in the previous paragraph does not lend itself to acceptable record-keeping. In today's regulatory environment, this form of development has become essentially obsolete. Sponsors are well aware that their developmental records are subject to extensive scrutiny during preapproval inspections (PAIs). Given that satisfactory completion of a

PAI is a prerequisite for ANDA approval, it is in the best interest of sponsors to ensure that formulation and process development follow a logical sequence. This is accomplished by way of the production of a series of "pilot" or "experimental" batches that ultimately lead to formulation and method of manufacture that will be documented in the ANDA. Experimental batches are usually quite small. They are manufactured in bench-top-scale production equipment and are used to do preliminary formulation work. Once a tentative formulation has been established, pilot batches may be manufactured in batch sizes between the experimental batch size and that required by the FDA for ANDA batches. Smaller versions of the production equipment to be used for commercial manufacturing are often used. If a pilot batch will be used for a pilot biostudy (a small study to determine if the formulation is promising), it must be manufactured using all appropriate cGMP controls.

The rationale for the chosen formulation and manufacturing process must be clear, and the sponsor must ensure that raw data from all pilot, experimental, and ANDA batches are preserved and maintained throughout the process. Formal development reports are a required part of the Common Technical Document ANDA format highly preferred by the FDA's Office of Generic Drugs and are necessary to assist the investigator during the PAI. Through narrative and presentation of data, these reports afford the ANDA sponsor the opportunity to guide the FDA reviewer and investigator through the process that was followed during development and define the key milestones that led to chosen formulation and method of manufacture.

Once the formulation and method of manufacture have been identified, it is advisable that the sponsor produce a confirmatory batch at the same scale as the exhibit batch that is intended to support the ANDA submission. This confirmatory batch enables the sponsor to identify and implement minor adjustments in processing parameters and controls before producing the batch that will be evaluated by the Office of Generic Drugs in determining the approvability of the ANDA.

The batches whose documentation is part of the ANDA may be called ANDA batches, submission batches, or exhibit batches. Throughout this chapter, we use these words as synonyms. Some of these batches are also biobatches, that is, the batches used in the pivotal biostudy or biostudies. However, not all submission batches are biobatches, because the FDA may grant a waiver, permitting the biostudy data from one strength of a product to be applied to a different strength of the same product. Although a waiver is granted, a batch must be produced and its documentation must be included in the ANDA.

This chapter will discuss the quality assurance (QA) and quality control (QC) requirements for pre-ANDA (commonly referred to as experimental, pilot, confirmatory batches) and ANDA batches. They include equipment, its qualification and calibration, documentation, optimization of process parameters, and justification of in-process specifications. We will also discuss development reports or logs and the FDA PAIs. Several regulatory requirements that vary according to scale and purpose of the batch are summarized in Table 7.1. They are discussed in more detail in the following pages.

TABLE 7.1
Regulatory Requirements for ANDA and Pre-ANDA Batches

		Batch	
Batch type	Experimental batch	Pilot/confirmatory batch	ANDA batch ("Biobatch")
Batch use	R&D only	Pilot biostudies/trial run before ANDA batch	Submission and any required biostudies
Equipment qualification or calibration	Essential elements (critical processing parameters)	Full	Full
Prevent cross-contamination	Limited	Yes	Yes
Documentation	Abbreviated batch record or laboratory notebook	Full batch record	Full batch record
Batch size	Smallest possible with equipment used	Intermediate for pilot/not less than 100,000 dosage units for confirmatory	Not less than 100,000 dosage units for ANDA pivotal bioequivalence study

EQUIPMENT

Often, research and development (R&D) personnel will argue that because the experimental batch will not be used in any biostudy or other human testing, and because the records and results will not be submitted to the FDA in the ANDA, the experimental batch does not need to be made using calibrated equipment. This can lead to problems further in the development sequence. The results obtained with the experimental batch will be used to make decisions about how to produce the pilot biostudy batch(es), if needed, and the ANDA submission batch(es). Use of unqualified or uncalibrated equipment may lead to erroneous conclusions and the establishment of process parameters that ultimately may not work. The purpose of Installation Qualification, Operational Qualification, Process Qualification, and Calibration are to ensure that the equipment is doing exactly what it is supposed to do. Hence, the essential elements of these processes must be performed on the equipment used to make experimental batches. By essential element, we mean all those functions that are part of the critical processing parameters, such as mixing speed or temperature, whose value has a substantial effect on the quality of the product. For equipment used to manufacture pilot batches to be used in pilot biostudies, complete qualification and calibration are required.

Requirements for prevention of cross-contamination are not the same for experimental batches as for later batches. For batches intended to be administered to humans (research subjects or patients), the sponsor must take steps to ensure that the level of cross-contamination is minimal. Acceptable levels are normally determined

by the toxicity of the compound in question. Because both equipment qualification and contamination control requirements for pilot biostudy batches approach those of submission and commercial batches, these types of batches are usually manufactured in production equipment. Larger firms may have a GMP R&D manufacturing facility for making these batches.

For experimental batches, cross-contamination must be low enough so that it does not alter the results of any measurements or tests performed on the batch. Because this level is usually many times higher than the threshold for batches administered to humans, equipment for experimental batches does not require isolation or stringent dust control. Many firms have a separate area for making such batches. This "pilot laboratory" has small versions of production equipment, usually contained within a single room. It is necessary to keep records of the cleaning of such equipment; however, QA sign off is not required.

DOCUMENTATION

Product development groups are strongly encouraged to have standard operating procedures (SOPs) that define how all activities are documented. Some firms use abbreviated batch records for experimental batches. These records may be completely or partially handwritten. They do not require QA or regulatory approval. Other firms prefer to document the preparation of an experimental batch in a laboratory notebook.

No matter which type of documentation the firm chooses, the records must clearly reflect what was done to produce the batch, all observations and test results, and a conclusion drawn from the results. The last item has, at times, been neglected by R&D departments. However, it is essential for reconstructing product development during an FDA PAI.

Pilot biostudy and submission batches must be manufactured under production conditions and cGMPs, with complete documentation. Complete documentation includes inventory records, batch records documenting every step in batch production, packaging records, analytical laboratory records (including retention of all raw data), and a certificate of analysis or analytical report. QA review and sign off are required. Firms should develop procedures that define prerequisite steps and requirements for release of such batches for biostudy testing.

OPTIMIZATION OF PROCESS PARAMETERS AND JUSTIFICATION OF IN-PROCESS SPECIFICATIONS

Since 1989, FDA investigators and reviewers have become more interested in optimization of process parameters and justification of in-process specifications. It is strongly advised that such activities be completed before ANDA submission batch manufacture. If the process is optimized at a later time, it will be necessary to amend master batch documentation to encompass the associated adjustments. This often leads to additional ANDA review cycles, which delay approval.

Due to Agency concerns about blend uniformity and for maximum efficiencies in manufacturing, blending times should be optimized. For example, if the R&D staff believes that 15 minutes of mixing is likely to work at a given step in the process, the best way to test this is to manufacture several experimental batches with different mixing times at that step, for example, 5, 10, 15, and 20 minutes. If there are several mixing steps in the process, testing all steps this way is not practical. The FDA will accept testing at the most critical mixing steps as a means of demonstrating uniform distribution of the drug. For solid dosage form manufacture, this is often the last mixing step, in which the lubricant is added. Many firms choose to use only one batch for mixing time studies, stopping the mixer every 5 to 10 minutes to sample the blend. Although, in theory, a batch mixed for four periods of 5 minutes is not the same as one mixed continuously for 20 minutes, the difference is usually insignificant. However, if there is any indication that the blend is prone to segregation or otherwise less than rugged, use of one batch is not advisable. In extreme cases, it may be necessary to test large numbers of finished dosage units to correlate blend uniformity to dosage form uniformity and optimize mixing times.

Experiments to establish the best method of sampling a given product blend for uniformity should be conducted early in the experimental batch process. If this is not done, errors due to sampling bias may confound conclusions about the effect of various process parameters on blend uniformity. A blend sample of adequate size should be taken using various techniques. The technique giving results that correlate with finished dosage uniformity should be selected [1–4].

In-process specifications such as unit weight and tablet hardness are justified by manufacturing product at or just outside the desired specification ranges. This material is tested for those attributes most likely to be affected by any deviation from specifications. For tablets, hardness is a parameter that may affect product quality by altering dissolution behavior. In most cases, dissolution decreases with increasing hardness. Therefore, tablets manufactured at the extremes of the desired hardness range are tested for dissolution profile. For a liquid product, or for solid products manufactured by processes including one or more solution steps, the pH of the solution may affect stability. For example, if the active ingredient is acid labile and the liquid product contains a buffer to keep the pH over 7, change in the buffer over time may lead to a decrease in the pH. The pH specification must take into account the maximum possible change in the buffer system. Samples manufactured at the pH extremes can be subject to accelerated stability conditions and tested for assay to confirm the specification limits. A similar approach can be used for processing and drying times of wet granulations.

It is not unusual for specifications and process parameters that work for a very small batch to be unsuitable for manufacture of a larger batch. Experiments to determine the effect of scale up are advisable for all but the simplest formulations. Scaling up in smaller increments, rather than from a few thousand dosage units directly to 100,000 is advisable.

The results of the testing described in the previous paragraphs and the conclusions drawn from these results should be presented in a report that is reviewed by Regulatory Affairs and QA. It is also advisable that firms include their manufacturing department in the review process, because it will ultimately inherit and be

responsible for executing the chosen method of manufacture on an ongoing basis to supply commercial need.

BATCH SIZE

Since 1990, the FDA has required that exhibit batches intended to support an ANDA submission comprise a minimum of 100,000 finished dosage units or 10% of the batch size intended for commercial production, whichever is greater [5]. The original basis for establishment of this standard is somewhat arbitrary; however, it has since proven to be an appropriate benchmark for scale-up operations.

DEVELOPMENT REPORTS OR LOGS

Generic drug firms prepare formal development reports for each product. Development reports outline the rationale for formulation development, summarize all the experimental batches made and what was concluded from the results obtained on them, explain what changes were made in the formulation during development, and list the processing parameters that were used for each batch.

A possible aid in the preparation of a Development Report is the use of a Development Log. A log is maintained for each project, showing the receipt of all raw materials, including samples for preliminary testing, testing done, experimental batches made, conclusions drawn, manufacturing and testing of the submission batches, and biostudy sampling. References to laboratory notebooks and other documentation are included. An example of a idealized Product Development Log is shown in Table 7.2. In larger R&D groups, which may have several projects ongoing

TABLE 7.2
Product Development Log for Profitabilamine Tablets, 1 mg code Number: P0022

Date	Action	Notebook References
01/07/97	Received raw material sample from Cornucopia Fine Chemicals	
01/14/97	Received technical dossier from Cornucopia Fine Chemicals	
01/28/97	Completed sample testing; material acceptable	RDP0022-1, pp. 1–10
01/31/97	Ordered 1.0 kg raw material from Cornucopia	
02/18/97	Material received from Cornucopia receiving number 97B055-P	
02/19/97	QA sample of 97B055-P received by laboratory	
02/20/97	Preliminary raw material analytical method approved	
03/06/97	97B055-P released by R&D laboratory	RDP0022-1, pp. 11–20
03/07/97	Experimental batch X005-C prepared in pilot lab; samples to R&D laboratory	
03/21/97	Dissolution of batch X005-C profile similar to brand batch 97XYZ09; uniformity and all other tests acceptable	RDP0022-1, pp. 25–35
03/25/97	Hardness. Thickness and weight specification report approved	
04/02/97	Master #P0022-1 for 100,000 tablet batch size approved	

at the same time, maintaining these logs is an ideal task for Project Managers separate from those individuals who make or test experimental or submission batches. Investment of a few minutes each day to make sure that the logs are complete and up-to-date will reap substantial benefits during the PAI.

PREAPPROVAL INSPECTIONS

According to the FDA's PAI Compliance Guide, the FDA will always conduct a PAI for the first ANDA (or NDA) submitted by a firm. The compliance program also requires an inspection for the first submission of a given product and for all submissions whose reference listed drug is one of the top 200 sellers in the United States. Whereas the firm's FDA District will almost always choose to do an inspection in the former case, it is somewhat less likely to do so in the latter. This may be because the Compliance Program does not specify which top 200 list to use or because the lists change from year to year [6]. For submissions that do not meet any of these criteria, the FDA District may choose not to inspect, if the firm has had an acceptable cGMP inspection in the last 2 years, and has demonstrated successful PAI history over the same time period. The District will simply tell the FDA Center for Drug Evaluation and Research, Office of Compliance that it has no objection to the approval.

What will the FDA look for during a PAI? The FDA investigators will verify the accuracy and completeness of key information in an ANDA submission during the inspection. They will examine bulk active ingredient purchase orders, invoices, and packing slips to ensure that the material was actually available to make the batch on the dates recorded in the batch record. If any of the inactive ingredients were not previously used by the firm, receiving records may be checked as well. The FDA investigators will compare the batch records in the submission to the use and cleaning logs for the equipment used to determine if the dates (and times, if recorded) match. Both of these activities are intended to rule out the possibility of falsified batch records.

The FDA investigators will also determine whether the firm has the equipment designated in the master batch records for commercial-size batches intended for manufacture after approval. This provision of the PAI program has historically generated the greatest number of recommendations to withhold ANDA approval among the various categories of required inspectional elements. In FDA summaries of reasons for a District not recommending ANDA or NDA approval, this deficiency is included in the failure category "plant not ready."

What is causing this problem? In many cases, a firm does not wish to purchase any equipment that will be unique to the commercial process of a submitted product until it is needed to start commercial production. The PAI generally occurs months or, in some cases, years before the ANDA is approved.

Fortunately for industry, FDA now has Scale-Up, Postapproval Changes (SUPAC) Guidances for various types of dosage forms [7] and a general guidance to changes permitted under the FDA Modernization Act of 1997 [8]. Firms may use these guidances to scale up a process without prior approval from the FDA. When a firm is introducing a new type of equipment in a submission, it is recommended that the scale-up information in the ANDA reflect the largest size batch that can be made on

the equipment used to make the submission batch, or other existing equipment, but not more than 10 times the size of the submission batch in dosage units. After ANDA approval, the firm can purchase and qualify larger equipment and use SUPAC to implement the production of larger batch sizes.

The FDA investigators will spend a lot of time during the PAI comparing the analytical data in the ANDA with that in the laboratory notebooks or other records. They often focus on any data that were rejected. Because the analytical methods used to test ANDA batches are generally new to the firm, unexpected method problems or chemist errors are not uncommon. The FDA is concerned that firms will reject valid data. Doing so may give an unrealistically favorable profile of the product. (The dilemma of when to properly reject laboratory data was one of the basic issues addressed in the "Barr Decision" [9].) Laboratory controls have become a very key element of PAIs. Much focus is placed on the handling of out-of-specification (OOS) test results. It is imperative that firms have written procedures in place regarding the investigation and ultimate disposition of OOS and other anomalous data. Often, a "decision tree" approach is used as the process can become complicated and the outcome can be dependent on a number of prerequisite steps including, but not limited to, sample reinjection, re-prepping and repeat testing, or, in extreme cases, batch resampling (Figure 7.1). Error simulation may be used as a means of confirming the cause of a suspect result and can add substantial weight to the overall quality of the investigation.

The ultimate disposition of a suspect result must be approved by the firm's QA unit after reviewing the associated investigation report. Thus, the investigating parties must ensure that the rationale for the proposed action is well documented and follows a logical sequence and that the data supporting the conclusions are referenced in the appropriate sections of the report.

On occasion, the FDA investigators have taken the position that the ANDA submission should contain reference to the existence of rejected data. Opinions among investigators vary on whether this is required for the submission to be complete or just something that makes the PAI easier. A firm should feel confident defending the exclusion of such references in its ANDA submission as long as the rationale for rejecting data is well justified, in compliance with its SOPs and has obtained QA approval. With this approach, the appropriateness of the firm's action becomes an issue for review during the PAI and does not unnecessarily complicate the application review process.

QA INVOLVEMENT IN R&D

Several generic drug manufacturers have found it useful to create a separate QA group for R&D. Members of this group receive special training so that they have a better understanding of the product development process. They are also free to concentrate on R&D without distraction or competition from the need to release other products for distribution. This practice can create efficiencies that have the effect of expediting the overall development, submission, and approval process. However, firms must be cautious in taking this approach. First, it is imperative to structure the reporting relationship such that a conflict of interest situation does not exist (i.e., this

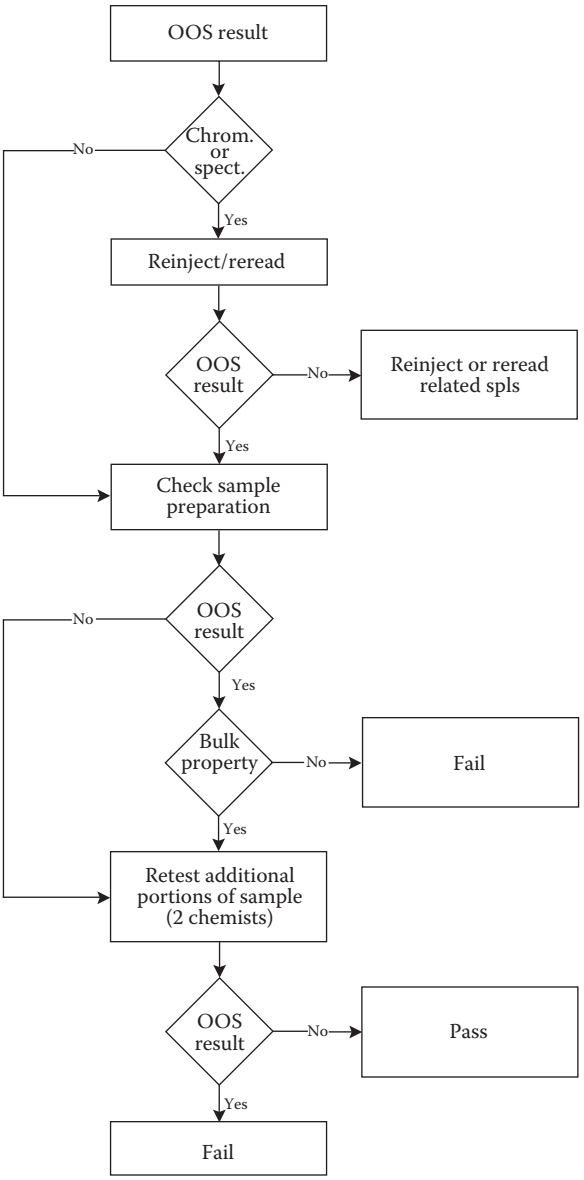

FIGURE 7.1 Decision tree for handling laboratory OOS results.

dedicated unit should report into the existing QA unit). Second, the policies and procedures of the dedicated unit should be consistent with those employed by the main quality unit.

Whether or not a firm chooses to establish a dedicated quality unit for R&D, the QA discipline must be involved in key activities of product development. Support for this involvement must come from the highest levels of management. Management

needs to take concrete steps to make this commitment clear to all. A QA audit of all relevant documentation while an ANDA submission is being prepared is strongly recommended if the firm wishes to have a successful PAI. However, this audit will be prone to problems and delays if QA has not been involved in checking the key elements of product development documentation on a regular basis. The audit will be most useful if it is performed by staff members who were not those doing the regular QA checks. Firms may opt to use outside consultants to perform presubmission audits. Although costly, this approach can often be justified by the anticipated reduction in overall approval time.

An issue related to those discussed in the previous paragraphs is the nature and timing of analytical method transfer from the R&D method development laboratory to the QC laboratory responsible for releasing approved products for marketing. The normal mechanism for this transfer is to have QC laboratory staff test samples of active ingredients, process intermediates, and finished product previously tested by R&D. Some firms opt to use samples that are prepared by R&D specifically for method transfer with known amounts of all analytes. This is a "safe harbor" approach intended to avoid the risks associated with practicing an analytical technique on an actual submission batch. If the prepared samples are powdered (made by accurately weighing all ingredients) while the dosage form is a tablet, a key step in the method is not tested. Extraction of the analyte can cause problems when the matrix is not sufficiently disintegrated. Preparation of compressed tablets from a small batch may be appropriate for simpler formulations but not for more complex ones. The use of submission batch samples for the method transfer experiments avoids these issues but introduces the risk of OOS results from the QC laboratory. Although the procedure is essentially a training exercise, the FDA investigators have been known to later question OOS results obtained during method transfer. If a firm opts to use submission batch samples for method transfer, it must ensure that any OOS results produced during the exercise are investigated in accordance with procedures previously discussed in this chapter (Figure 7.1).

Timing of method transfer often depends on available QC resources. A firm may choose to perform the transfer after ANDA approval and may even use the first scale-up batch as transfer testing material. The degree of risk assumed with this approach increases with the complexity of the product and/or the analytical method.

Some firms have chosen to transfer the methods to QC before manufacture of the submission batch. An experimental or pilot batch with the same formulation and manufacturing process as anticipated for the submission batch is used as testing material. This approach enables the resolution of method-related issues before the generation of supporting data for the submission batch. Here, a firm can reduce the time to approval by avoiding additional review cycles otherwise warranted by method revisions identified later in the process.

A large number of firms choose a middle course. When Regulatory Affairs declares that all major FDA observations related to the submission have been resolved, plans are made to manufacture commercial batches and validate the scaled-up process. Method transfer is conducted while the materials needed for the scale-up are on order, so that the QC laboratory is ready to test the process validation samples for the commercial batches when they are available. Firms that opt to take

this approach must have a substantial degree of confidence in the robustness of their methods. Otherwise, late fixes may be required and the ANDA submission will have to be amended.

CONCLUSION

As the information in this chapter demonstrates, QA and QC oversight is an essential part of generic drug development. Firms that establish and follow sound procedures and practices for drug development and ensure proper quality oversight throughout the process will reap the benefits of successful PAIs and timely ANDA approvals. Although resource intensive, this approach can provide substantial commercial advantage and significant contribution to the "bottom line."

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8 Drug Product Performance: In Vitro*

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* Opinions expressed in this chapter are those of the authors and do not necessarily reflect the views or policies of the FDA.

INTRODUCTION

The chapter examines the issues related to the in vitro characterization of solid oral dosage forms. The importance and utility of in vitro characterization are discussed in relation to the factors influencing in vitro drug release, including those intrinsic to the drug substance, the drug product and manufacturing process, and the relevant dissolution test methodology. A discussion is also provided on practical issues that may be faced during the conduct and evaluation of in vitro dissolution testing and the application of in vitro drug product performance testing.

IMPORTANCE OF IN VITRO DRUG PRODUCT CHARACTERIZATION

Modern solid oral dosage forms are expected to be of high quality and exhibit reliable performance characteristics. This is achieved by careful selection and quality control of various ingredients and a well-defined manufacturing process, giving careful thought to different variables that may influence product appearance, potency, uniformity, purity, stability, and dissolution. In modern pharmaceutics, as the complexity of materials, instruments, equipment and techniques have increased, it has become imperative to apply up-to-date research methods, techniques, and tools to manufacture and monitor these dosage forms. In vitro characterization of solid oral dosage forms is important from the perspective that it provides us with information regarding the rate at which the active ingredient is released from the dosage form. This characterization is vital for formulation development, comparability assessment, and product performance.

In vitro testing to characterize the potency, uniformity, and release rate of the active ingredient(s) in solid oral dosage forms is based on the monographs and general chapters in the United States Pharmacopoeia (USP)/National Formulary [1] and on various guidance of the U.S. Food and Drug Administration (FDA) [2–4]. Tests and requirements for content and consistency of the dosage form include assay or potency of the active ingredient(s) and content uniformity/weight variation of dosage units. Tests for in vitro release of active ingredient(s) from the dosage form include dissolution and disintegration.

After oral administration of a solid oral dosage form, the critical elements of drug absorption are (a) disintegration and dissolution and (b) permeation across the membranes of the gastrointestinal tract. Due to the critical nature of the first of these steps, in vitro dissolution is often relevant to the prediction of in vivo drug product performance. This is particularly true for low solubility drugs and for modified-release (MR) dosage forms, for which dissolution/drug release is usually the rate-limiting step in the in vivo absorption.

TYPES OF SOLID ORAL DOSAGE FORMS

Among the different types of solid oral dosage forms available, tablets and capsules are the most popular and constitute a major share of the market. Tablets are often variously categorized as regular (oral), effervescent, chewable, orally disintegrating, etc. Capsules may be of either the soft or hard gelatin variety. Examples of less

common solid oral dosage forms are powders, granules, chewing gum, troches, and wafers.

The solid oral dosage forms may also be categorized by their release characteristics. The two types are immediate-release (IR) and modified release (MR). The IR products are designed to release their active ingredient(s) promptly after administration. The MR products comprise delayed-release (DR) dosage form (enteric-coated) and extended-release (ER) dosage form (also referred to as controlled-release, sustained-release, etc.).

DR products are formulated to retard release of the active ingredient until the dosage form leaves the stomach. This is done to protect the gastric mucosa from drug irritation, to limit exposure of acid-labile drugs to stomach acid, or to target release of the active ingredient to the lower intestinal tract to enhance in vivo absorption. Often, DR dosage forms have an enteric polymeric coating with characteristic pH-dependent solubility (or stability) to prevent release of the active ingredient in the stomach at low acidic pH. Once the DR product leaves the stomach, the enteric coating dissolves (or is degraded); subsequent in vivo drug release then generally follows the same course as for an IR product.

ER products are formulated to make the active ingredient available over an extended period of time. These ER products that comprise sustained-release, controlled-release, and repeat-action varieties are expected to lengthen the dosing interval and reduce the dosing frequency compared with the corresponding IR product [5,6]. This is achieved to enhance patient convenience/compliance, to increase therapeutic effectiveness, and/or to help minimize toxicity or side effects, especially in those products for which a rapidly released dose, or drug level fluctuations, might not be desirable.

FACTORS AFFECTING IN VITRO DRUG PRODUCT DISSOLUTION

The process of drug product dissolution can be viewed as proceeding through several discrete steps. The first of these involves the wetting and penetration of the dissolution medium into the dosage unit. The second step, which generally occurs in many conventional dosage forms, but certainly not a prerequisite for dissolution, involves disintegration and/or deaggregation into granules or fine particles of the drug substance. The third step involves the solubilization of the drug substance into the solution. These steps need not proceed in a stepwise manner and can occur simultaneously during the dissolution process.

In vitro drug product dissolution can be affected by various factors, including those intrinsic to the drug substance, the drug product formulation, the manufacturing process, and the dissolution testing methodology, as individually discussed below.

Factors Related to Drug Substance

Dissolution refers to the process of solubilization of the drug into the dissolution medium. As a fundamental process, dissolution is controlled by the affinity between the solid and the dissolution medium [7] and can be modeled as the diffusion of the

drug into the bulk liquid media. Noyes and Whitney [8] in 1897 proposed a fundamental equation for dissolution:

$$dm/dt = K \times (C_s - C_t). \tag{8.1}$$

Here, dm/dt is the mass rate of dissolution, K is the proportionality constant called the dissolution constant, C_s is the concentration at saturation or maximum solubility, and C_t is the concentration at time t. The term $C_s - C_t$ in the above equation represents the concentration gradient between the diffusion layer and the bulk solution. In 1900, Brunner and Tolloczko [9] modified the above equation by incorporating the surface area S:

$$dm/dt = K' \times S \times (C_s - C_t). \tag{8.2}$$

Here, K' is a constant unique to the chemical substance and varies widely from drug to drug.

Brunner expanded the scope of the above equation to include Nernst's (1904) theory [10] of a saturated and stagnant liquid film diffusion layer of thickness h around the drug particle, having a diffusion coefficient D in a bulk dissolution volume V:

$$dC/dt = [DS/Vh] \times (C_s - C_t). \tag{8.3}$$

From these theoretical principles, it is quite apparent that drug dissolution is influenced by solubility, diffusivity, surface area, and solution hydrodynamics.

Solubility of the Drug Substance

The dissolution rate of a drug is closely associated with drug substance solubility. Compounds with high solubility generally exhibit significantly higher dissolution rates as shown in Equation 8.3. The solubility of compounds containing "ionizable groups" is a function of the pH of the dissolution media and the pKa of the compound. Solubility of a drug is traditionally determined using an equilibrium solubility method and involves suspending an excess amount of solid drug in a selected aqueous medium. In some cases, it may not be feasible to measure the equilibrium solubility of a compound, such as for a metastable polymorph that undergoes conversion during the time frame of the solubility measurement. In this instance, a dynamic method may be used to estimate the solubility of the compound. This is referred to as kinetic solubility and is generally determined by measuring the intrinsic dissolution rate [11].

The FDA's BCS guidance (please see Ref. [49]) considers a drug substance "highly soluble" when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5. The "dose/solubility" ratio of the drug provides an estimate of the volume of fluids required to dissolve an individual dose. When this volume exceeds approximately 1 L, in vivo dissolution is often problematic [12]. For example, griseofulvin has an aqueous solubility of 15 μg/mL and at a dose of 500 mg has a dose/solubility ratio of 33.3 L. This therefore exhibits a dissolution/solubility limited oral absorption.

Polymorphism

The drug substance may also exist in different physical forms and exhibit solid-state polymorphism. Polymorphism refers to a drug substance

1. Existing in two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice
2. Having differing hydrate (or other solvate) forms
3. Having amorphous phases that do not possess a distinguishable crystal lattice [13,14]

Difference in the lattice energies of these polymorphs result in differences in the solubility and hence in the dissolution rate of these various polymorphic forms [15]. The solubility differences between different crystalline polymorphs will typically be less than several-fold, and in the case of hydrates, these generally exhibit lower solubilities than the anhydrous form. In the case of amorphous forms, these can have solubilities several hundred times that of the corresponding crystalline counterparts [16]. It is well known for quite some time that the amorphous (noncrystalline) forms, in general, tend to dissolve faster than the crystalline forms. As early as 1960, Mullens and Macek* showed that the amorphous form of novobiocin has a greater solubility and higher dissolution rate than the crystalline form, which were substantiated by the blood level data. Polymorphism in chloramphenicol palmitate is another example. Chloramphenicol palmitate can exist in two polymorphic forms: Form A and Form B. Form B is shown to exhibit greater oral absorption than Form A due to enhanced solubility [17].

Salt Factor and "pH" of the Diffusion Layer

In general, organic salts are more water soluble than the corresponding unionized molecule and this offers a simple means of increasing dissolution rate. It is for this reason that sodium and potassium salts of weak acids, as well as hydrochloride or other strong acid salts of weak bases, are frequently selected during drug development. A multitier approach to select salts for achieving optimal product performance is discussed in the literature [18].

In addition, even if the equilibrium solubility of the parent drug and the salt in the dissolution medium may be alike, the dissolution rate of the salt of the weak acid or base will often be enhanced. This effect can be explained based on differences in the pH of the thin diffusion layer surrounding the drug particle [19]. In the case of salts of free acids, the pH of the diffusion layer will be greater than the pH of the diffusion layer for the acid. Analogously, in the case of salts of the free base, the pH of the diffusion layer will be less than the pH of the diffusion layer for the free base. This will result in higher effective solubilities of these salts in the diffusion layer compared with their parent unionized compounds and in an increased dissolution rate. The salt occasionally may be useful for another therapeutic indication. For example, the nonsteroidal anti-inflammatory drug naproxen [20] was originally marketed as a free acid for the treatment of rheumatoid or osteoarthritis. However, the sodium salt,

* Mullens and Macek (1960). *J. Am. Pharm. Assoc. Sci. Ed., 49*, 245.

which is absorbed faster than the acid, was found to be more effective in postpartum pain than the parent compound.

Surface Area and Particle Size

The dissolution rate of a compound is also directly related to its exposed surface area (as is evident from Equation 8.3). Therefore, drug particle size reduction, which results in an increased surface area exposed to the dissolution medium, would be expected to increase the dissolution rate. Hence, micronized formulations of poorly soluble drugs may exhibit markedly increased rates of dissolution compared with nonmicronized formulations [19]. This is evidenced in marketed formulations of products such as glyburide tablets. The micronized formulations (e.g., Glynase tablets) dissolve much faster than the nonmicronized formulations (e.g., Micronase tablets).

Formulation Factors

The inactive ingredients (excipients) used in the formulation may also have an important effect on drug product dissolution. In the case of IR dosage forms, excipients are often used to enhance dissolution rates. For example, disintegrants such as cross-carmellose sodium and sodium starch glycolate are used to facilitate breakup of the tablet dosage form and promote deaggregation into granules or fine particles [21]. The effect of the disintegrant is to promote tablet deaggregation and expose a greater drug particle surface area, thereby facilitating dissolution. Surfactants, such as sodium laurel sulfate and polysorbate, may also be used to accelerate dissolution rates. This effect of the surfactant is achieved by increasing the aqueous solubility of hydrophobic drugs by micelle formation, and/or by facilitating drug wetting, by decreasing the surface tension of the hydrophobic drug particle with the dissolution media and thereby creating a larger drug–solvent surface interface for dissolution to occur [22,23]. Hydrophilic binders and fillers may also be incorporated into the formulation to promote wetting of hydrophobic drug particles to enhance dissolution rates [22].

Conversely, excipients may sometimes have an inadvertent retarding effect upon drug dissolution. For example, during formulation development, care must be taken to ensure that the drug does not bind to an excipient, such as in the formation of an insoluble metal chelate that may alter the drug dissolution profile. Lubricants such as the stearates, which are commonly used to decrease friction in the die wall cavity, are generally hydrophobic in nature, and at high concentrations (>1%), these may have the effect of reducing drug wettability [22,24]. This will have the effect of prolonging disintegration times or in diminishing the effective interface of drug particles with the solvent medium, resulting in reduced dissolution rates. Gelatin capsule shells are prone to cross-linking in the presence of free aldehydes or keto groups. This may result in pellicle formation and a greatly reduced dissolution rate. This type of phenomenon has been attributed to the dissolution failures seen with gelatin capsules and gelatin-coated tablets packaged with rayon fillers [25].

For MR drug products, the excipients are chosen to have a controlled effect on the rate of drug release from the dosage form, to target the delivery to certain sites

along the gastrointestinal tract, commonly referred to as the "absorption windows." This can be achieved by dispersing or incorporating the active ingredient into a hydrophilic or hydrophobic matrix, ion-exchange resin, osmotic pump, or by coating the drug particles or the dosage unit with a polymeric or wax film. These MR dosage forms are formulated by a complex process that must take into consideration the properties of the active ingredient, the type of release device that is to be used, the characteristics of modifying release excipients that may be chosen, and the desired drug release profile that is to be achieved [26].

Manufacturing Process Factors

Several manufacturing variables can affect the drug product dissolution characteristics. Here, manufacturing strategies may be employed to enhance dissolution rates. For example, spray drying or melt extrusion of the active ingredient with excipients such as polyvinylpyrrolidine can be used to generate stabilized amorphous dispersions, which have greatly accelerated dissolution rates [19,27]. Improved wetting of hydrophobic drug surfaces and enhanced dissolution rates are sometimes achieved by employing wet granulation versus dry granulation processes during product manufacture [28]. Direct compression may also be chosen over granulation for enhancing dissolution based on the propensity for directly compressed tablets to deaggregate into finer drug particles [29].

Conversely, manufacturing variables may also have a retarding effect upon dissolution. For example, overmixing with lubricants may have an adverse effect on drug wettability and hence upon drug disintegration and dissolution [19]. Tablet punch pressures must also be optimized to achieve acceptable disintegration rates [30]. At low punch pressure, liquid penetration in the tablet will be facile, but disintegrant swelling may not result in tablet deaggregation due to its high porosity; on the contrary, excessive punch pressure may hinder the penetration of liquid into the tablet and result in slower disintegration rates.

For the IR and MR products, the manufacturing process must be well defined and be highly robust to assure reproducible drug release from batch to batch. Here, the process of dispersing the drug into the matrix or of coating the drug with MR excipients must be tightly controlled. The manufacturing process must have well-defined "endpoints" and must distribute the MR excipients uniformly around the active ingredient; otherwise, this will be reflected in variable dissolution performance [31].

Dissolution/Drug Release Test Conditions

Dissolution test parameters such as apparatus type and rotation speed [32] and dissolution medium pH and volume [22] can also significantly influence the dissolution rate of a solid oral dosage form. The dissolution test conditions are discussed in greater detail below in Sections Dissolution Test—IR Solid Oral Dosage Forms and Drug Release Test—MR Solid Oral Dosage Forms. The dissolution assay method and adequate instrumentation are important to generate valid measurements of the dissolution process.

IN VITRO DRUG PRODUCT PERFORMANCE EVALUATION

Disintegration Test

The disintegration test is described in the USP General Chapter <701> *Disintegration*. Disintegration testing is considered appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. It is a qualitative test and does not quantify drug dissolution. An official disintegration apparatus, the USP basket-rack assembly, is used to perform the test, which is generally applicable only to IR products. The International Conference on Harmonization (ICH) Q6A Guidance document [33] has proposed a decision tree for the application of the disintegration test. When product dissolution is rapid (defined by ICH as dissolution NLT 80% in 15 min at pH 1.2, 4.0, and 6.8) and the dosage form contains drugs that are highly soluble throughout the physiologic range, disintegration testing may be meaningful. The ICH Guidance considers a drug substance to be "highly soluble" when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1.2 to 6.8. The volume estimate of 250 mL is derived from a typical bioequivalence study protocol that prescribes administration of a drug product to fasting human volunteers with a glass (~8 ounces) of water.

Dissolution Test—IR Solid Oral Dosage Forms

The dissolution test is referenced in USP General Chapter <711> *Dissolution*. The test quantitatively measures the amount of active drug that dissolves from the dosage form in a liquid dissolution medium using standard dissolution apparatus and procedures. The FDA's general recommendations regarding dissolution testing are given in the Agency's Guidance *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* [2]. The dissolution test is required for virtually all solid oral dosage forms as a condition of product approval. The ICH Q6A Guidance document [33] provides three decision trees for assisting in the development of suitable dissolution test conditions and tolerances. The dissolution test conditions are generally selected to ensure a sensitive and discriminatory measure of drug product performance [34]. As discussed later in the chapter, dissolution data can also be used to support certain postapproval changes in manufacturing and/or formulation as well as to waive the requirement to conduct in vivo bioequivalence studies under certain conditions.

1. **Apparatus:** USP General Chapter <711> *Dissolution* establishes equipment specifications and operational standards for the Apparatus 1 (basket) and Apparatus 2 (paddle), the apparatus most commonly used for studying the dissolution of solid oral dosage forms. The basket at 100 rpm is commonly used for testing capsules and the paddle at 50 rpm for tablets. The dissolution rate generally increases as the stirring rate or dissolution speed is increased. This increase, however, may not necessarily follow a simple mathematical relationship [32]. The USP Apparatus 3 (see USP General Chapter <724> *Drug Release*) is also sometimes used for dissolution testing of IR drug products in addition to ER products [35]. Apparatuses 4 and 7

are used exclusively for ER dosage forms, including oral tablets and capsules. For convenience, the official USP apparatus used for dissolution/drug release testing of solid oral dosage forms, along with their recommended operational parameters and target drug products are given in the following table:

USP Apparatus	Description	Rotational Speed	Dosage Form
1	Basket	50–120 rpm	IR, DR, ER
2	Paddle	25–100 rpm	IR, DR, ER
3	Reciprocating cylinder	6–35 dpm[a]	IR, ER
4	Flow-through cell[b]	N/A	ER and poorly soluble APIs in IR
7	Reciprocating disk	30 cpm[c]	ER

[a] 6–35 dips per minute currently in approved USP monographs; other speeds may also be acceptable.

[b] USP Apparatus 4 currently not used in any USP monograph (dissolution or drug release test).

[c] 30 cycles per minute currently in approved USP monographs; other speeds may also be acceptable.

2. **Media:** The selection of a dissolution test medium is based on the physicochemical properties of the drug substance and characteristics of the dosage form. In selecting the medium, an attempt should be made to emulate physiologic conditions. Thus, media with pH values ranging from 1.2 (gastric pH) to 6.8 (intestinal pH) are generally preferred. The most common media used in dissolution testing are 0.1 N hydrochloric acid, pH 4.5 acetate buffer, and pH 6.8 phosphate buffers. For drugs that are weak acids, the dissolution rate increases with increasing pH, whereas, for weak bases, the dissolution rate decreases with increasing pH. Selection of appropriate medium volume (generally 500–1000 mL, with 900 mL being the most common) is primarily based on drug solubility. For drugs with poor aqueous solubility, a larger volume may be necessary to achieve sink conditions and complete drug dissolution in a reasonable amount of time. Alternatively, surfactants may be added to the dissolution medium. The incorporation of surfactants into the dissolution medium generally enhances solubility and dissolution rate through reduction of the interfacial tension and induction of micellar formation. Addition of ionic salts to the dissolution medium also may increase the dissolution rate, but the use of hydroalcoholic or any other media containing organic solvents is discouraged. For hard and soft gelatin capsules and gelatin-coated tablets, specified quantities of enzymes may be added to the dissolution medium to prevent the formation of pellicles that may result from crosslinking of gelatin [1]. Also, tiny air bubbles can circulate in the medium and affect the uniformity of hydrodynamics of the test. The air can be removed from the medium by the deaeration method described in

USP <711> *Dissolution* or another validated method. The temperature of the dissolution bath is usually maintained at 37°C ± 0.5°C to reflect human body temperature. Currently, new research efforts are being made on the use of "biorelevant" media to predict the dissolution of poorly soluble drugs and to predict plasma levels of lipophilic drugs [36,37].

3. **Acceptance Criteria:** The dissolution test acceptance criteria or "tolerances" are specified in terms of the quantity ("Q") that is dissolved within a specified time interval. The quantity is expressed as a percentage of the "labeled claim" (and not the assayed amount) of active ingredient in the dosage form. Typically, for most IR oral dosage forms, 80% ("Q") of the labeled amount of the active drug ingredient is specified to be dissolved within a set time duration (test times between 15 and 60 min are most common). The dissolution test results are evaluated using the Acceptance Table in USP <711>, which describes criteria for mean and individual sample dissolution results through three progressive stages of testing (S_1, S_2, and S_3, specifying 6, 12, and 24 samples tested, respectively). The value specified for "Q" should be used "as is" and should not be confused with the "Q+5%" value specified for the S_1 stage of testing. Drug products may meet the dissolution requirement at any stage of testing; however, for bioequivalence purposes, the stage S_2 testing (at least 12 units testing) is recommended. The dissolution tolerances are initially established based on the dissolution profiles obtained from the drug product lot(s) upon which the in vivo bioavailability/equivalence study was performed. The initial specifications can be revised later, if necessary, as more data become available. A generic IR drug product should generally meet the dissolution requirements specified in the USP monograph. If no USP requirements are established, the product should be formulated to meet or exceed the in vitro dissolution performance of the Reference Listed Drug (RLD), as identified in the FDA "Orange Book" [6]. Characteristics such as drug solubility, permeability, dissolution rate, and pharmacokinetics should be considered in setting dissolution test specifications in order for the test to be useful in ensuring product similarity/equivalence.

Drug Release Test—MR Solid Oral Dosage Forms

The drug release test is analogous to the dissolution test, except that it is applied to MR drug products rather than to IR drug products. The FDA's general recommendations regarding drug release testing are given in its Guidances: *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* and *Extended Release Oral Dosage Forms: Development, Evaluation and Application of In vitro/In vivo Correlation*. As in the dissolution test, the test for drug release is conducted on sample sizes of 6 to 24 individual dosage units (at least 12 dosage units are required for bioequivalence testing). Owing to differences in release mechanisms among ER drug products, the products for a given drug type made by different manufacturers are allowed to have unique drug release tests and do not necessarily have to use the tests approved for the RLD or other manufacturers. If a USP drug release method is not available for the extended-release dosage

form and an FDA recommended method is available, then it is expected that the drug release be conducted using the FDA recommended method. Whether additional drug release testing would be required depends on the product formulation. For multiple strengths of ER tablets and capsules, where the various strengths are not produced from a "common blend," additional drug release testings are needed on all strengths. Given this, however, unjustified proliferation of tests should be avoided. The recommended test apparatus, media, and tolerances are discussed in detail below.

1. **Apparatus:** For MR oral dosage forms, the USP (in General Chapters <711> and for transdermal products <724>) provides equipment specifications and operational standards for the Apparatuses 3, 4, and 7 in addition to Apparatuses 1 and 2 (see the table in Dissolution Test—IR Solid Oral Dosage Forms). Use of Apparatuses 1 and 2 is usually preferred, however, for solid oral dosage forms, unless there is a demonstrated advantage in using another official apparatus. The use of nonofficial apparatus is generally discouraged.
2. **Media:** The media are generally the same as those recommended for testing IR products, except that there is no provision for the addition of enzymes (two-tiered testing). For DR (enteric-coated) solid oral dosage forms, a two-stage procedure is as follows: first, testing in 0.1 N HCl for 2 hours to demonstrate acid resistance followed by testing in pH 6.8 buffer. The acid-stage and buffer-stage tests each have their own Acceptance Table in the USP General Chapter <711> (see below).
3. **Acceptance Criteria:** Release acceptance criteria are proposed based on the in vitro drug release performance of the biostudy lot or lots. The acceptance criteria should include a minimum of three time points selected from within the labeled dosing interval. The first acceptance range is set at early time point to ensure against "dose dumping." Subsequent time points are also established as ranges and the final time point is set as a minimum value of labeled amount released (e.g., NLT 80%). The criteria are generally interpreted according to the Acceptance Table 2 in the USP General Chapter <711> for ER dosage forms and Acceptance Tables 3 and 4 for DR dosage forms. Three levels of testing are described, similar to those for the IR drug products.

Dissolution/Drug Release Profile Comparisons

For adequate and complete characterization of dissolution, several FDA guidances request submission of comparative multitime point dissolution profile data in addition to meeting a single-point tolerance ("Q") requirement [2,3,38,39]. Several different profile comparison approaches (such as model-dependent, model-independent multivariate, and model-independent index) have been developed and evaluated [40–43]. These approaches are useful for comparing the dissolution profiles of drug product lots, especially to evaluate the effects of scale-up, postapproval changes (SUPAC).

In the model-dependent approach, the profile similarity is evaluated using a model specified by a suitable mathematical function to describe the dissolution data.

The approach is recommended for the dissolution "data-rich" scenarios. After selecting a model, the dissolution profiles are evaluated in terms of model parameters. The approach is exercised through the following steps:

1. Select a suitable mathematical function (model) to describe the dissolution data at hand (say, coming from a few production-size pre-change lots).
2. Fit the individual unit dissolution data from different standardized production-size lots to the selected model and estimate the interlot and intralot variability of the model parameters.
3. Define a "similarity region" or criterion based on the interlot and intralot parameter variance.
4. Fit the dissolution data from "N" units of the reference (say, pre-change) and test (say, post-change) lots using the same mathematical function to generate model parameters.
5. Calculate a "statistical distance" between parameter means of the test and reference lots.
6. Compute a 90% "confidence region" around the statistical distance.
7. Compare the "confidence region" with the "similarity region" calculated in step 3 to assess the similarity or dissimilarity of the profiles.

If the confidence region computed from step 6 falls within the bounds of the similarity region generated in step 3, the profiles are considered similar, else they are considered dissimilar. A comprehensive discussion of this approach is beyond the scope of this chapter. For a detailed and hands-on discussion of this approach, the readers are directed to Refs. [40,41].

In the model-independent "multivariate" approach, the dissolution values are compared directly without assuming a model or creating parameters. Each dissolution measurement, coming from the multiple dissolution time points is considered as a variable, correlated to adjacent time points. First, a "statistical distance" is computed, which accounts for the mean dissolution differences as well as their variance, covariance matrix. A confidence region is then computed around the statistical distance. The statistical distance often used for this type of (multivariate) analysis is known as "Mahalanobis distance" or "M-distance." It is given by the formula

$$D_M = \sqrt{[(X_2 - X_1)' S_{\text{pooled}}^{-1} (X_2 - X_1)]}, \tag{8.4}$$

where D_M = "Mahalanobis distance," $S_{\text{pooled}} = (S_1 + S_2)/2$ is the sample variance–covariance matrix pooled across both the test and reference batches, where S_1 and S_2 are the variances for the Reference and Test, respectively, X_1 is the mean dissolution of Reference, and X_2 is the mean dissolution of Test. For a detailed discussion of the approach, readers are directed to ref. [42].

In the index approach, profiles are compared with respect to a particular a priori defined index. Several indices have been proposed, such as "Rescigno" in 1992 [44], fit factors "f_1" and "f_2" by Moore and Flanner in 1996 [45], and Rho, Rho-m, Delta-a, and Delta-s by Seo et al. [46]. Various FDA guidances recommend the use of "f_2"

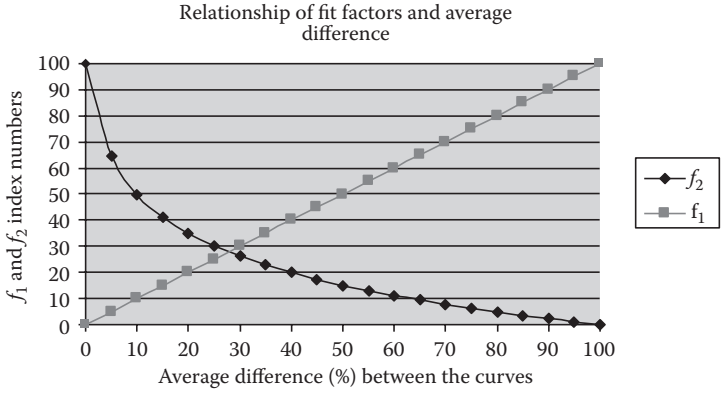
index, renamed "similarity factor" [38], for mean dissolution profiles comparison due to simplicity and ease. The f_1 and f_2 indices, which measure the overall difference and similarity between the two profiles, are defined as follows:

$$f_1 = \left[\left(\sum_{i=1}^{P} |\mu_{ti} - \mu_{ri}| \right) \Big/ \sum_{i=1}^{P} \mu_{ti} \right] \times 100 \tag{8.5}$$

and

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{P} \sum_{i=1}^{P} (\mu_{ti} - \mu_{ri})^2 \right]^{-0.5} \times 100 \right\}. \tag{8.6}$$

In the above expressions, μ_{ti} and μ_{ri} are the means of the test and reference at the *i*th time point and *P* is the number of time points. The "f_1" index is the cumulative absolute mean difference of the dissolution points normalized to the cumulative reference. It is thus a measure of relative error between the two curves. The "f_2" index is a function of the reciprocal of the mean square root transform of the sum of squared differences at all points. Essentially, it is the sum of squared error arranged on a logarithmic scale. When the two profiles are exactly identical, f_1 = 0 and f_2 = 50 × log (100) = 100. When one product dissolves completely before the beginning of dissolution of another product, f_1 becomes 100 and f_2 becomes = $50 \times \log \left\{ \left[1 + (1/P) \sum_{i=1}^{P} (100)^2 \right]^{-0.5} \times 100 \right\} = -0.001$, which can be approximated to 0. The f_1 and f_2 indices therefore can be considered as scaling between approximately 0 and 100. A relationship of average (global) difference and corresponding f_1 and f_2 index values is given in the following graph.



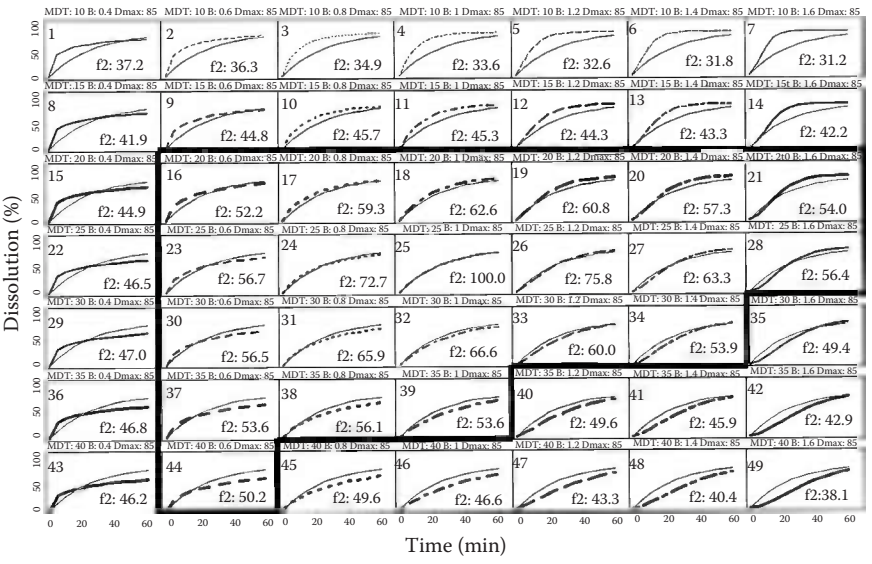
As seen from the graph, the greater the "f_2" or smaller the "f_1," the more similar are the two profiles. An "f_2" value between 50 and 100 suggests a less than 10%

global or overall difference between the two dissolution profiles. Due to its global nature, the "f_2" index acquires certain advantages and disadvantages. The advantages include simplicity, ease of calculation, and unbiased estimation with respect to the position of test sample points to reference points. The limitations include omission of interlot or intralot variability, as well as covariance estimation, nonconsideration of positional or directional differences, and a bias with respect to the number of sample points and their selection. Also, although useful to a great degree for evaluating SUPAC, the f_2 is of limited value for products having a permeability-limited absorption. In these cases, f_2 failure (value >50) becomes meaningless. In 1998, Shah et al. [43] evaluated f_2 as a population measure and discussed the statistical properties of the estimate based on sample means. It was pointed out that the commonly used f_2 from the sample means is a biased and conservative estimate of the population f_2.

There is an important issue in the dissolution profile comparison using f_2—the practical significance of differences between mean dissolution profiles. That is, how large can the difference between mean dissolution profiles be before the differences are likely to impact on in vivo performance?

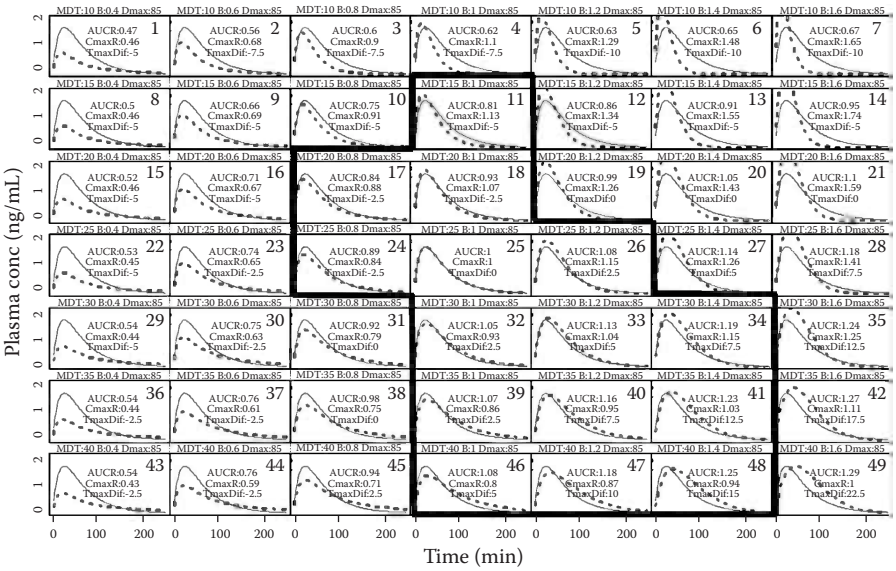
Knowing how consistent f_2 similarity is with the criteria for bioequivalence is important for assuring similarity in product performance. It is necessary to address the following two questions: (a) how likely the two products determined to be similar in vitro are not bioequivalent (false positive) and (b) how likely the two products determined to be dissimilar in vitro are bioequivalent (false negative).

A study was initiated to investigate the consistency between the in vitro dissolution profile comparisons using an f_2 matrix and in vivo bioequivalence using the 80% to 125% criteria for an extended-release formulation [47]. The study utilized a simulation approach to examine several potential scenarios to get a general picture about this issue. The following figure exemplifies a set of simulated dissolution profiles.



In the figure, the solid lines in each panel are the dissolution profiles for the reference product, whereas the dashed lines are those for the test product. As seen, when the parameters of the test and reference used for simulation are the same, the profiles of the reference and test are exactly overlapped (panel 25 with f_2 of 100). However, as the parameters of the test product deviate from those of the reference, the profiles of the test product may be higher (top panels, such as panel 4) or lower than the reference (bottom panels, such as panel 46). In some other instances, the early parts of the test profile are higher, whereas the later parts are lower than the reference profile (panels on the left, such as panel 22) or vice versa (panels on the right, such as panel 28). The f_2 values are labeled in each panel, which are smaller when the parameters deviate further. Those values less than 50 are colored red and thick black lines are drawn to separate those similar from dissimilar.

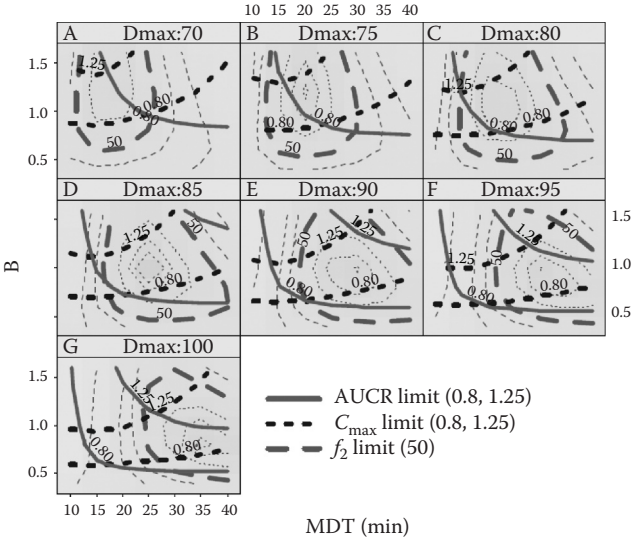
For each dissolution profile, the in vivo concentration profile is predicted using an in vitro/in vivo correlation (IVIVC) model. The corresponding in vivo profiles for the dissolution profiles shown above are presented in the following figure. In each panel of the figure, the ratios of area under the curve (AUC) and C_{max} (and T_{max} difference) between the test and the reference are shown. Thick black lines are drawn to separate those bioequivalent from bio-nonequivalent.



This study demonstrated the general consistency between in vitro dissolution comparison using the f_2 factor and in vivo bioequivalence. The results also indicate that dissolution profiles that are judged similar using the f_2 factor may not always be bioequivalent when tested in vivo. On the other hand, in vitro dissolution profiles judged dissimilar by the f_2 factor may sometimes generate in vivo bioequivalent profiles. As shown in the following figure, the Weibull parameter range used for generating the dissolution profiles, which are determined to be similar to the reference profile by f_2 factor, is called f_2 similarity region (enclosed by

thick dashed lines) whereas the parameter range generating in vivo profiles, which are bioequivalent to reference profile, is called bioequivalence region (enclosed by solid lines for area under the curve and dotted lines for C_{max}). It can be seen that the f_2 similarity region and the bioequivalence region are close, although they do not exactly match.

This study emphasizes the importance of evaluating the shape and the completeness of in vitro dissolution curves when f_2 is used to determine the similarity between different formulations because the completeness of dissolution relates to the extent of drug absorption in vivo and the shape of a dissolution curve is translated to the rate of drug absorption in vivo. In particular, when there is a difference of more than 10% in the plateau levels between dissolution profiles of the test and reference product or when the two dissolution profiles cross, there is a greater likelihood for the test product to be not bioequivalent to the reference product, although f_2 similarity has been demonstrated. Under these circumstances, caution must be exercised in drawing conclusions.



APPLICATIONS OF IN VITRO DISSOLUTION

Product Development

In vitro dissolution is an important and useful tool during the development of a dosage form. In vitro dissolution often aids in guiding the selection of prototype formulations and for determining optimum levels of ingredients to achieve drug release profiles, particularly for extended-release formulations. In vitro testing also guides in the selection of a "market-image" product to be used in the pivotal in vivo bioavailability or bioequivalence studies.

Quality Assurance

A dosage form must possess acceptable in vivo bioavailability or bioequivalence performance characteristics. After pivotal in vivo studies, in vitro dissolution testing methodology and acceptance criteria are devised based on dissolution testing of these biolots as well as upon the current knowledge of drug solubility, permeability, dissolution, and pharmacokinetics. This in vitro dissolution testing is then performed on future production lots and is used to assess the lot-to-lot performance characteristics of the drug product and provide continued assurance of product integrity/similarity.

Product Stability

In vitro dissolution is also used to assess drug product quality with respect to stability and shelf-life. As products age, physicochemical changes to the dosage form may alter the dissolution characteristics of the drug product over time. For example, as the moisture level increases or decreases over time, this can result in altered tablet hardness and subsequent possible changes in dissolution characteristics. For some products, polymorph transformations to more stable and hence less soluble crystalline forms may result in reduced dissolution rates. As mentioned previously, for gelatin-encapsulated drug products, aldehyde-amino cross-linking over time may result in pellicle formation that also slows the dissolution rate [48]. As in vitro dissolution testing is performed for products throughout their shelf-life, this type of testing provides assurance of adequate product performance throughout the expiry period.

Comparability Assessment

In vitro dissolution is also useful for assessing the impact of preapproval or postapproval changes to the drug product, such as changes to the formulation or manufacturing process. Various "SUPAC Guidances," depending on the nature and extent of these changes, recommend either a single-point dissolution or dissolution profile comparison(s) to evaluate the effect of these changes. This type of in vitro comparability assessment is critical to ensure continued performance equivalency and product "similarity."

Waivers of In Vivo Bioequivalence Requirements

In vitro dissolution testing or drug release testing may be used for seeking waiver of the requirement to conduct in vivo bioavailability or bioequivalence studies in conjunction with the following.

Formulation Proportionality

In situations where an in vivo bioavailability and bioequivalence study is conducted on the highest strength of the drug product, in vivo bioavailability and bioequivalence testing on the lower strength(s) of the same dosage form may be waived, provided that the lower strength(s) are proportionally similar in their active and inactive ingredients and that their dissolution profiles have sufficient similarity [3,49].

It is also possible to get a waiver for a higher strength based on the similarity of dissolution profiles provided the following conditions are met: (a) clinical safety and/or efficacy data on the proposed dose and the need for the higher strength, (b) linearity of the pharmacokinetics over the therapeutic dose range, and (c) the higher strength is compositionally proportionally similar to the lower strength that has bioavailability data.

The guidance [3] defines "proportionally similar" in the following ways:

- All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50 mg strength has all the inactive ingredients, exactly half that of a tablet of 100 mg strength and twice that of a tablet of 25 mg strength).
- Active and inactive ingredients are not in exactly the same proportion between different strengths as stated above, but the ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.
- For high-potency drug substances, where the amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within ±10% of the total weight of the strength on which a bio-study was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.

Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) categorizes drug substances into four classes: High Solubility/High Permeability (Class I), Low Solubility/High Permeability (Class II), High Solubility/Low Permeability (Class III), and Low Solubility/Low Permeability (Class IV). A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5. A drug is considered highly permeable when extent of absorption (fraction of dose absorbed, not systemic bioavailability) in humans is determined to be greater than 90% of an administered dose based on a mass balance determination or in comparison with an intravenous reference dose. An IR drug product is also characterized as a "rapidly dissolving" product when not less than 85% of the labeled amount of the drug substance dissolves within 30 min using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 mL or less of each of the following media: (a) acidic media, such as 0.1 N HCl or USP simulated gastric fluid without enzymes; (b) a pH 4.5 buffer; and (c) a pH 6.8 buffer or USP simulated intestinal fluid without enzymes. If the drug product meets the BCS criteria for Class I, meaning that the drug substance is highly soluble and highly permeable, and the drug product is rapidly dissolving, it is quite likely that the rate-limiting step for drug absorption is gastric emptying. In this instance, the requirements for in vivo bioavailability or bioequivalence

studies for this product can be waived [49]. BCS is thus a useful approach for which the FDA has issued a guidance [50]. As of July 2012, 37 drug substances have been found to be eligible for BCS I classification, allowing their oral products to be considered for biostudy waivers. Attempts have also been made [51] to ascertain the maximum absorbable dose using information such as solubility, transintestinal absorption rate constant, small intestine water volume, and transit time.

In Vitro/In Vivo Correlations

After a formulation is developed, meaningful in vitro dissolution in conjunction with techniques such as deconvolution can be used to establish an in vitro/in vivo relationship that is able to predict in vivo dissolution and absorption. These relationships between in vitro drug release and in vivo absorption (level "A," "B," or "C" correlation) are generally more likely for drugs exhibiting low solubility and high permeability (BCS Class II) and for ER products. When these IVIVCs have been established, in vivo bioavailability or bioequivalence studies, which are normally required, may be waived [4]. Polli [52] recently suggested development of an objective criterion to identify models a priori to IVIVC analysis.

LIMITATIONS OF IN VITRO DISSOLUTION

This chapter has focused on the general utility of dissolution testing. Nonetheless, the limitations of this methodology cannot be overlooked. The precision and accuracy of dissolution testing is often dependent on several subtle operational controls, including stirring element eccentricity, agitation alignment, torsional vibration, dosage form position, sampling position, dissolved gases, flow patterns, and heat transfer, among other factors, which if overlooked, may have a large effect upon the dissolution measurement. This is exemplified by a recent study demonstrating dramatically different dissolution rates arising from changes in tablet position, which are attributed to the segregation of solution hydrodynamics in the dissolution testing apparatus [53]. Therefore, strict observance of these many subtle factors are essential to assure reliable and reproducible test results.

Another limitation is that, in the absence of a suitable IVIVC, dissolution testing may not be particularly relevant to drug product performance. In the case of IR products containing BCS Class I and Class III drugs, dissolution testing may be "overdiscriminating" because its oral absorption is likely to be limited by gastric emptying or intestinal permeation. On the other hand, in the case of IR products containing BCS Class II and IV drugs, single-point dissolution testing may be "nondiscriminating" and hence may not be able to detect lots having poor in vivo performance. In addition, even when an IVIVC has been developed, this will likely be of limited value as such correlations are often "product specific."

Despite these apparent limitations, dissolution testing remains one of the most important and useful in vitro tests for assuring product quality. It is only by recognizing these limitations that one can make judicious conclusions regarding the significance or insignificance of a dissolution test result as it pertains to product performance. Recognizing these limitations will also enable the development of more meaningful and useful dissolution testing methodology.

FUTURE DIRECTION

With advances in technology and increased understanding of in vivo absorption, often dissolution methods that have clinical or in vivo relevance can be developed such that the method may provide more mechanistic information lending to greater product understanding. Implementation of Quality-by-Design principles into drug development efforts and availability of the FDA/ICH Quality guidance documents support advancing in vitro methods into reliable benefit/risk assessment tools linking in vitro and in vivo product performance and patient benefit.

Computer modeling can be effectively used to enhance the understanding of the in vitro and in vivo dissolution of a target oral dosage form. The desired attributes of the product can be studied and sensitivity of different physicochemical and physiologic parameters affecting the in vivo release could be ascertained a priori. A model such as Advanced Compartmental Absorption and Transit can be coupled with the regular compartmental or physiologic model [54] to map the drug lifecycle from its in vitro release to the in vivo input, absorption, distribution, metabolism, and elimination phases. Computer modeling and simulations can be targeted to cover aspects such as deconvolution, in vitro/in vivo relationship, drug transport, and bioavailability.

SUMMARY

During early discovery, and various stages of drug development, reliable in vitro dissolution testing may provide significant product information and, if shown to have in vivo relevance, could be used for guiding product development and may even replace some in vivo clinical trials. However, use of in vitro dissolution methods and leveraging of the information gained from in vitro studies vary greatly. In vitro dissolution testing has been evolving over the years from use as a product quality characterization tool to serving as a link between in vitro and in vivo product performance. When applicable, dissolution testing serves as a surrogate for bioequivalence demonstration as well as an indicator of a well-controlled, robust, and reliable manufacturing process, delivering products with established batch-to-batch consistency.

From the product quality perspective and for adequate assurance of in vivo performance of a solid dosage form, a detailed in vitro characterization is essential. In vitro dissolution testing of the solid oral dosage form can be conducted using various tests and techniques. This type of evaluation is useful during product development, for quality assurance and control, for product stability testing, and during assessment of comparability. In vitro dissolution testing may also be useful for getting waivers of in vivo bioavailability or bioequivalence studies, particularly when the dosage form exhibits formulation proportionality to the biostudied lot, or when the drug meets the criteria for BCS Class I and exhibits rapid dissolution, or when a meaningful in vitro/in vivo relationship is established. The modern frontiers in developing efficient in vitro performance testing include areas such as fiber optics for monitoring of drug concentration in the dissolution medium [55], application of artificial neural network for dissolution prediction [56], and process analytical technology [57].

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9 ANDA Regulatory Approval Process

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The U.S. Food and Drug Administration (FDA) is organized into nine offices/centers: the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Food Safety and Applied Nutrition, the Center for Veterinary Medicine, the National Center for Toxicological Research, the Office of the Commissioner, the Center for Tobacco Products, and the Office of Regulatory Affairs.

The CDER reviews the safety and efficacy of drug products. The Office of the Center Director oversees 12 offices, which include the Office of Pharmaceutical Science, the Office of New Drugs, the Office of Executive Programs, the Office of Surveillance and Epidemiology, the Office of Management, the Office of Regulatory Policy, the Office of Medical Policy, the Office of Counter-Terrorism and Emergency Coordination, the Office of Communications, the Office of Compliance, the Office of Translational Sciences, and the Office of Planning and Informatics. Additional information about the organization of the CDER can be found on the FDA website at www.fda.gov/cder.

Organizationally, the Office of Generic Drugs (OGD) is located within the CDER under the Office of Pharmaceutical Science. It consists of the following divisions: Chemistry, Bioequivalence, Clinical Review, Microbiology, and Labeling and Program Support. The following will provide a brief overview of the history of the OGD.

Nearly 30 years after its enactment, the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch–Waxman Amendments (HWA), has proven to be an effective piece of legislation. One outcome of this legislation is the increased availability of less expensive medications to millions of Americans. The HWA to the Federal Food, Drug and Cosmetic Act (FD&C) gave

clear statutory authority to submit abbreviated new drug applications (ANDAs) for all approved innovator drugs. With the passage of the HWA, firms who sought to market a generic version of a drug were not required to repeat the costly preclinical and clinical testing associated with a new drug application (NDA).

The OGD had its origins in the early 1970s and was known as the Office of Drug Monographs. After the passage of the HWA in 1984, the Office of Drug Monographs became the Office of Drug Standards. The Office of Drug Standards contained the Division of Generic Drugs and the Division of Bioequivalence (DB). The OGD as we know it today was established in 1990 as part of the Office of Pharmaceutical Science. Its mission is to ensure that safe and effective generic drugs are available for the American people. The OGD ensures the safety and efficacy of generic drugs by employing a review process that is similar to the NDA process. The primary difference between the Generic Drug Review process and the NDA review process is the study requirements. For example, an ANDA generally requires a bioequivalence study between the generic product and the reference listed drug (RLD) product. The safety and efficacy of the RLD product were established previously through animal studies, clinical studies, and bioavailability studies. Thus, these studies need not be repeated for the ANDA.

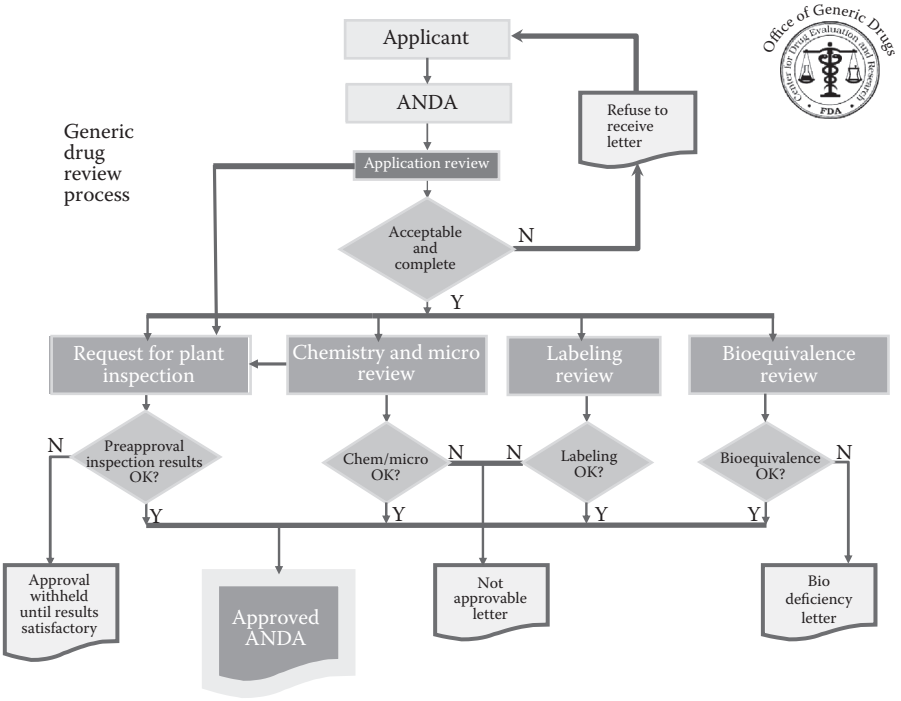


FIGURE 9.1 Generic drug review process.

The economic impact of the HWA is best demonstrated by the increased market share of generic medications. In 1984, just 14% of all prescriptions dispensed were for generic drugs. In contrast, 27 years later in 2011, approximately 78% of all prescriptions dispensed were for generic drugs. Furthermore, with the use of generic drugs, consumers save roughly $3 billion per week. Since the inception of HWA to date, generic drugs have saved the American healthcare system over $1 trillion.

The goal of this chapter is to provide an overview of the generic drug review process for solid oral dosage forms. Each step of the review process will be discussed from the initial submission of the application to its final approval. As one reads through the chapter, it may be useful to refer to the flow diagram given in Figure 9.1. Because the discussion is limited to the review of solid oral dosage forms, the microbiology review is omitted.

FILING REVIEW OF ANDA

The ANDA process begins when an applicant submits an ANDA to the OGD. The document room staff processes the ANDA, assigns it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA checklist.

Within the first 60 days after the submission of an ANDA, a filing review is completed. The Regulatory Support Branch (RSB) is responsible for the filing review. This group, organized under the Division of Labeling and Program Support (DLPS), consists of project managers and a support staff, including technical information assistant(s), legal instruments examiner(s), and consumer safety technician(s). The branch chief who reports to the Division Director of DLPS supervises the branch.

The RSB ensures that the ANDAs contain the information necessary to merit a technical review. To determine whether an application is acceptable for filing, an RSB project manager (RPM) compares the contents of each section of the application (see Appendix 9.A) against a list of regulatory requirements. An applicant may receive a "refuse to receive" letter for a number of reasons. These include, but are not limited to, when an inactive ingredient level exceeds the level previously used in an approved drug product via the same route of administration, incomplete bioequivalence studies, incomplete stability data, incomplete packaging, and incorrect basis for submission. The filing date of an application is critical because it may determine the eligibility for exclusivity. The RSB verifies that all applications contain a patent certification and exclusivity statement. The patent certification and exclusivity statement must address all existing patents and exclusivities for the RLD published in the "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book." If an RLD has expired patents, an applicant may certify that no relevant patents remain. The review of patents and exclusivities is an ongoing process throughout the review cycle, as new patents and exclusivities may become listed in the "Orange Book." An explanation of patent certifications with their corresponding definitions may be found in 21 CFR 314.94(a)(12).

Once the RSB completes the filing review of the ANDA and verifies that the application contains all the necessary regulatory requirements, an "acknowledgment" letter is issued to the applicant indicating its acceptance for filing and the official filing date. The application is then assigned to the technical reviewers. If the ANDA does not meet the criteria for filing, a "refuse-to-receive" letter is issued to the applicant with a list of deficiencies.

Upon filing an ANDA, the RPM forwards an Establishment Evaluation Request to the Office of Compliance. The Office of Compliance then determines if the drug product manufacturer, the drug substance manufacturer, and the outside testing facilities are operating in compliance with current Good Manufacturing Practice (cGMP) regulations as outlined in 21 CFR Parts 210 and 211. Each facility listed on the request is evaluated individually and the Office of Compliance makes an overall evaluation of all facilities listed in the application. Furthermore, a preapproval inspection may be performed to assure the data integrity of the application.

Currently, ANDAs can be submitted entirely electronically via the Electronic Submissions Gateway. Applicants can also submit electronic submissions of bioequivalence data along with the traditional paper application. The electronic document room staff processes the electronic files, so that the reviewers can access them. The data contained in the electronic submission are copied onto the CDER's computer network. Additional processing may occur to populate the electronic tools used by the reviewers.

All applicants who plan to submit ANDAs electronically should consult CDER's website for electronic submissions at www.fda.gov/ForIndustry/ElectronicSubmissions Gateway//default.htm.

COORDINATION OF THE GENERIC DRUG REVIEW PROCESS

Once the ANDA is accepted for filing, the application enters the review queue. This means that the application is assigned to a bioequivalence division and team, a chemistry team, and a labeling reviewer.

Each chemistry team consists of a team leader, a project manager, and several reviewers. In this section, the emphasis will be placed on the chemistry project manager's role in the generic drug review process.

The chemistry project manager serves as the "application" project manager (APM). Although APMs are located within the chemistry review teams, they are actually a part of the Review Support Branch within the DLPS. Specifically, they plan, organize, and coordinate all of the review activities for the applications that they manage. This requires the coordination of all discipline reviews, which include chemistry, bioequivalence, labeling, and sterility assurance (microbiology) for sterile products. Furthermore, the APMs monitor the compliance evaluation (field inspections) of all the facilities associated with the ANDA to assure they are in compliance with cGMP requirements. The APMs serve as coleaders for the chemistry review teams. They assure timely resolution of scientific and regulatory conflicts to prevent delays in the review process. The APMs also make every effort to meet the review goals set by the OGD management.

The APMs manage and coordinate the work of the review teams to assure that reviews are performed in a timely manner. In addition, the APMs identify and resolve potential problems such as the inequality of individual workload and regulatory issues. The OGD makes a concerted effort to comply with the statutory 180-day review cycle mandated by the Federal FD&C Act. The APMs play a key role in coordinating the various disciplines to review the applications within 180 days from the submission date. In attempt to achieve the OGD's management goals, the APMs may recommend redistribution of work according to the policies and procedures within the OGD.

The APMs enter key information about their applications into various databases, including the Document Archiving, Reporting & Regulatory Tracking System and the Establishment Evaluation System. These databases allow the OGD staff to access the status and outcome of discipline reviews and the status of the field and compliance inspection reports. The APMs use the information to provide applicants and OGD management the status of applications.

Because communication plays a large role in the generic drug review process, the APMs are designated as the primary contacts for all issues relating to the review of the application. As such, they communicate the status of all aspects of the applications that they manage. The APMs attempt to address all applicant inquiries within 2 working days of receiving a request. If the questions from the applicant are of a technical nature and require further evaluation by a reviewer and/or team leader, the APMs make the appropriate arrangements for either a telephone conference or a meeting. The APMs generally request applicants to submit a proposed agenda before the telephone conference or meeting. The APMs and the review teams work with the applicants to resolve scientific issues that may delay the approval of applications.

BIOEQUIVALENCE REVIEW PROCESS

After an ANDA is accepted for filing by the RSB, the bioequivalence section is assigned to one of the DBs to review based on the therapeutic category of the drug product. The bioequivalence project managers (BPM) access a list of pending ANDAs and assign them to individual reviewers according to the "first-in, first-reviewed" policy. Typically, the dissolution testing portion of the submission is assigned and reviewed before that of the bioequivalence study. The BPMs also randomly assign other review documents such as bioinvestigational new drug applications (bio-INDs), protocols, and correspondence.

The DB's responsibilities include the review of the bioequivalence section of ANDAs, supplemental ANDAs, bio-INDs, protocols, and controlled correspondence. Structurally, the DB is organized into 10 review teams; each team consists of approximately five reviewers, who are supervised by a team leader. The team leaders complete a secondary review of all bioequivalence submissions assigned to their team. In addition, they ensure the consistency of the recommendations provided to the applicants. A BPM is assigned to each team and is responsible for processing all

reviews and managing the bioequivalence review process. A statistician is also available to resolve statistical issues.

The bioequivalence review process establishes bioequivalence between a proposed generic drug and the RLD. Bioequivalence is established when the ratio of the means of the test product compared with the reference product (T/R) of the pharmacokinetic parameters for rate (C_{max}) and extent of absorption (AUC) of log-transformed data meet the 90% confidence intervals of 80% to 125%. Refer to Chapters 10 and 11 for a more detailed discussion of bioequivalence testing requirements and statistical considerations.

The BPMs provide regulatory guidance on bioequivalence issues through correspondence and teleconferences. In addition, the BPMs coordinate the resolution of all regulatory and scientific issues regarding the bioequivalence of drug products submitted for marketing approval. All meetings and teleconferences regarding bioequivalence issues are scheduled and documented by the BPM.

The BPMs request and track inspections of the clinical and analytical sites through the Office of Scientific Investigations (OSI). Inspection requests to the OSI are sent immediately after the ANDA is assigned to a reviewer. The clinical and analytical sites are inspected for two reasons: (1) to verify the quality and integrity of the scientific data submitted in bioequivalence studies and (2) to ensure that the rights and welfare of human subjects participating in the studies are protected in accordance with the regulations (21 CFR 312, 320, 50, and 56). Significant problems, such as research misconduct or fraud (see MaPP 5210.7) are promptly acted upon. One of the most common findings on an OSI inspection is the absence of retention samples by the testing facility (refer to 21 CFR 320.38 and 320.63 and the draft guidance "Handling and Retention of BA and BE Testing Samples" for more information). If problems are discovered during these inspections, additional studies from the applicant may be requested.

If a bioequivalence reviewer requires additional information to complete their review, they will first consult with their team leader and then request the BPM to obtain the information from the applicant. If an issue can be resolved within 10 working days, a teleconference with the applicant is initiated by the BPM. The BPM maintains a record of all teleconferences with the applicants. The applicant's response to the teleconference is labeled as a "Bioequivalence Telephone Amendment—Response to Information Request." A deficiency letter is issued to the applicant when a review contains numerous deficiencies that require more than 10 days to resolve.

The reviewer prepares a draft or primary review, which is then forwarded to the team leader for a secondary review and/or revisions. During the secondary review, the team leader provides comments on the primary review, discusses regulatory or scientific issues with the Division Director or Deputy Division Director, and assesses the need for additional data from the applicant. Once all unresolved or outstanding issues are addressed, the team leader sends the review back to the reviewer with his comments. The reviewer then finalizes the review and forwards it to the Division Director. The Division Director or Deputy Division Director performs a tertiary review and documents concurrence.

Once the bioequivalence review is completed and all bioequivalence requirements are addressed, the DBE archives an acceptable letter that states that there are no further questions at this time. Additionally, the APM is notified electronically that the bioequivalence review is complete. If the bioequivalence review indicates deficiencies, a deficiency letter is issued to the applicant.

Bioequivalence studies with clinical endpoints are often recommended to establish bioequivalence between dosage forms intended to deliver the active ingredient(s) locally (i.e., topical creams and ointments) and between dosage forms that are not intended to be absorbed (i.e., rifaximin tablets, 200 mg) (21 CFR 320.24(b)(4)). The OGD's Director, Division of Clinical Review (DDCR) and the clinical team review these studies for the DB. The DDCR also forwards all comments and recommendations to the Director of the DB for concurrence. The DDCR consults with the Office of New Drugs for input on the appropriateness of clinical endpoints (see MaPP 5210.4). For this reason, it is strongly advised that applicants submit protocols or bio-INDs before the initiation of bioequivalence studies with clinical endpoints to ensure the appropriateness of study designs and endpoints (see MaPP 5240.4).

CHEMISTRY REVIEW PROCESS

After an ANDA has been accepted for filing by the RSB, the Chemistry, Manufacturing and Controls (CMC) section of the application is assigned to the appropriate Chemistry Division and Team based on the therapeutic category of the drug product. Once the application is assigned to the team, the application is designated as "random" and placed on the team leader's queue. The APM assigns the application to a reviewer on his or her team according to the "first-in, first reviewed policy." The Chemistry Divisions review the CMC section of ANDAs, Drug Master Files, Supplemental ANDAs, Annual Reports, and Controlled Correspondence.

The Chemistry Divisions are organized into review teams consisting of five or six primary reviewers, a team leader, and the APM. Team leaders perform a secondary review of all chemistry submissions. An APM assigned to each team coordinates the entire review process and acts as the primary point of contact for the application. Each division is led by a Division Director and Deputy Director. A tertiary review is often performed by the Deputy Director, but may be performed by the Division Director, to ensure consistent recommendations to applicants. Interdivisional consistency is also emphasized through regular meetings between the Chemistry Divisions and the OGD management.

The goal of the chemistry review process is to assure that the generic drug will be manufactured in a reproducible manner under controlled conditions. Areas such as the applicant's manufacturing procedures, raw material specifications and controls, sterilization process, container and closure systems, and stability data are reviewed to assure that the drug will perform in an acceptable manner.

The chemistry reviewer drafts a primary review that is forwarded to the team leader for secondary review. The secondary review may require little or no revision from the first draft or it may require major revision. Team leaders provide comments and corrections to the primary reviewer. The APM also assists in the correction

process. Once the team resolves the issues internally, the review is finalized and signed by the team leader, the primary reviewer, and the APM. The finalized review, including a list of deficiencies, is forwarded to the Deputy Director for concurrence. The Deputy Director or, in some cases, the Division Director completes the tertiary review. After all issues are resolved within the Chemistry Divisions, it is the responsibility of the APM to communicate the status of the application to the applicant. After the chemistry deficiencies are classified as either "minor" or "major," the deficiencies are communicated (usually by fax) to the applicant. When the chemistry portion of the application is ready for approval, the approval package is assembled by the APM and routed for the final administrative reviews through the office. The Chemistry Divisions coordinate with all of the review disciplines for each application to make sure each portion of the application is acceptable before approval.

LABELING REVIEW PROCESS

After an ANDA has been accepted for filing by the RSB, the Labeling section of the application is assigned to the appropriate labeling reviewer based on the therapeutic category of the drug product. The Labeling Review Branch is part of the DLPS. A team leader oversees the work of four to six reviewers.

The basis for the labeling review is to ensure that the generic drug labeling is the "same as" the RLD labeling. There are several exceptions to the "same as" regulation. Exceptions are allowed for the following: differences due to changes in the manufacturer or distributor, unexpired patents, or exclusivities and other characteristics inherent to the generic drug product, such as tablet size, shape, or color.

The labeling reviewer also identifies and resolves concerns that may contribute to medication errors. For example, the labeling reviewer may identify drug names that are similar or that sound alike. In addition, the labeling reviewer may address concerns associated with the prominence and/or legibility of drug names on a container label. To ensure that the proposed labeling in an ANDA is the "same as" the RLD, the labeling reviewer must first identify the RLD. The next step is to find the most recently approved labeling for the RLD. If the RLD labeling is not the most recently approved, it is considered discontinued labeling. Hence, it is not acceptable for the labeling review. It is very important to monitor FDA's database and website on a regular basis to determine the most recent labeling approvals.

One allowed difference between the generic and the RLD labeling is the omission of information protected by patents and exclusivity. The labeling reviewer ensures that the applicant properly addresses all patents and exclusivities by verifying the information in the "Orange Book." The applicant's patent certification and exclusivity statement determines the way the proposed labeling will be drafted.

The applicant may submit 4 copies of draft labeling or 12 copies of final printed labeling as proposed labeling. Draft copies may also be submitted for tentative approval. The labeling branch supports the submission of electronic labeling. This practice is preferred and strongly encouraged.

For United States Pharmacopeia (USP) products, the labeling reviewer uses the USP to evaluate the established name, molecular structure, molecular weight, structural formula, chemical name, and the storage conditions of the proposed drug product.

As the container label or carton label is reviewed, the labeling reviewer decides if the labeling is easy to read and positioned in accordance with the regulations. In addition, the labeling reviewer encourages applicants to revise their labeling to decrease the likelihood of confusion with other drug products.

After completing the review of the proposed labeling, the labeling reviewer drafts a review that either identifies labeling deficiencies or recommends approval. A tentative approval may be issued for an application with outstanding patent and exclusivity issues. The team leader completes a secondary review of the application. If he or she is in agreement with the review, the review is sent back to the labeling reviewer to finalize. The labeling reviewer then forwards the review back to the team leader for concurrence.

If the proposed labeling is deficient, the APM or the labeling reviewer communicates the deficiencies to the applicant. If the proposed labeling is acceptable, an approval or tentative approval summary is forwarded to the APM.

PUTTING IT ALL TOGETHER

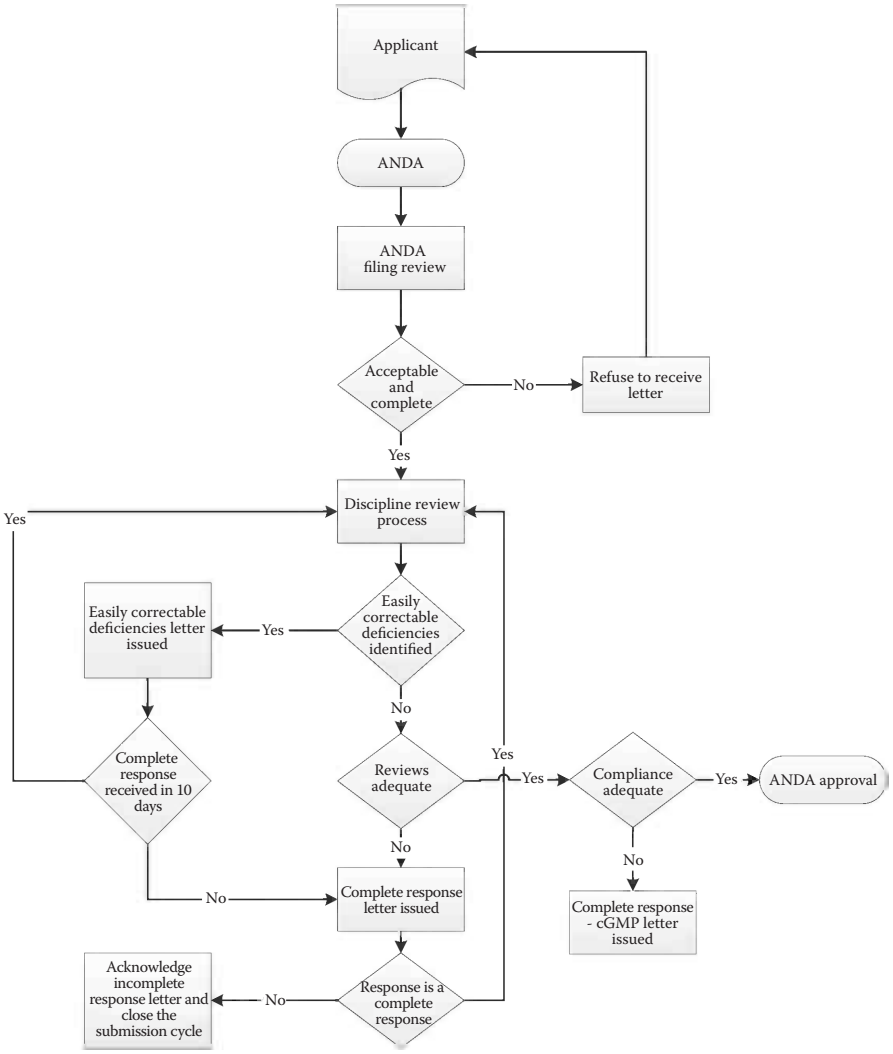
After the final office-level administrative review, where all individual disciplines have resolved their deficiencies and all of the facilities associated with the ANDA have received an acceptable compliance evaluation, the application will either receive a full approval or a tentative approval letter (see ANDA Approval Chart).

The APMs are instrumental in assembling an approval package. This package includes all reviews supporting final or tentative approval. When the review of an ANDA is completed, the APMs draft the appropriate approval letter and circulate it with the reviews and application for concurrence. The APMs communicate with the OGD management on a weekly basis to update them on the progress of reviews.

A full approval letter details the conditions of approval and allows the applicant to market the generic drug product. A tentative approval letter is issued if there are unexpired patents or exclusivities accorded to the RLD. The tentative approval letter details the circumstances associated with the tentative approval and delays the marketing of the product until all patents and/or exclusivities expire. Once the Office Director or his designee has signed the final approval letter, the APM calls and faxes a copy of the approval letter to the applicant. The document room staff then mails the final approval letter to the applicant.

As one can see, the generic drug review process incorporates a series of checks and balances to ensure the integrity of the reviews. The OGD is comprised of bioequivalence reviewers, chemists, labeling reviewers, microbiologists, medical officers, and project managers. These individuals work together as a team to accomplish the OGD's mission of providing safe and effective generic drugs to the American People.

APPENDIX 9.A ANDA REVIEW PROCESS



- An ANDA is received by the OGD.
- Once an ANDA is found acceptable for filing, the discipline review process will begin.
- Throughout the discipline review process, easily correctable deficiencies (ECD) may be identified; if ECDs are issued, the ANDA applicant has 10 federal government business days to respond.
- Responses to ECD that are incomplete or partial will be incorporated in a Complete Response (CR) letter with all remaining deficiencies from all pending review disciplines.
- Once a CR letter is issued, the review cycle is considered closed.

- The applicant must address all deficiencies in the CR letter in order for another discipline review process to begin.
- A compliance portion of the ANDA must be found acceptable in addition to each adequate discipline review status to be eligible for an approval.
- If all discipline reviews are found adequate but an ANDA is noncompliant with cGMP regulations, a Complete Response Action letter is issued.

10 Bioequivalence and Drug Product Assessment: In Vivo

Barbara M. Davit and Dale P. Conner

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INTRODUCTION

No topic seems so simple but stimulates such intense controversy and misunderstanding as the topic of bioequivalence. The apparent simplicity of comparing in vivo performance of two drug products is an illusion that is quickly dispelled when one considers the difficulties and general public misunderstanding of the accepted regulatory methodology. One sometimes hears members of the public and medical experts alike stating various opinions on the unacceptability of approved generic drug products based on misconceptions regarding the determination of therapeutic equivalence of these products to the approved reference. These misconceptions include the belief that the U.S. Food and Drug Administration (FDA) approves generic products that have mean differences from the reference product of 20% to 25% and that generic products can differ from each other by as much as 45%. In addition, some incorrectly assume that bioequivalence testing in normal volunteers does not adequately reflect bioequivalence and therefore therapeutic equivalence in patients. When the current bioequivalence methods and statistical criteria are clearly understood, it becomes apparent that these methods constitute a strict and robust system that provides assurance of therapeutic equivalence. In this chapter, we will discuss the history, rationale, and methods utilized for the demonstration of bioequivalence for regulatory purposes in the United States. In addition, we will touch on the challenges of determining bioequivalence of locally acting oral drug products.

OBJECTIVES OF BIOEQUIVALENCE STUDIES

The most important concept in the understanding of bioequivalence is that the sole objective is to measure and compare formulation performance between two or more pharmaceutically equivalent drug products. Formulation performance is defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance and eventually leading to one or more pharmacologic effects, both desirable and undesirable. If equivalent formulation performance from two products can be established, then the clinical effects, within the range of normal clinical variability, should also be equivalent. This is the same principle that leads to an equivalent response from different lots of the brand-name product.

Generic drug products must be both pharmaceutically equivalent and bioequivalent to be considered therapeutically equivalent and therefore approvable. Pharmaceutical equivalents must contain the same amount of the same drug substance and be of the same dosage form with the same indications and uses. Thus, an immediate-release tablet would not be considered pharmaceutically equivalent to an oral liquid suspension, capsule, or modified-release tablet. Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when administered at the

same molar dose under similar conditions in an appropriately designed study. Two drug products are considered therapeutically equivalent if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. The FDA believes that products classified as therapeutically equivalent can be substituted for each other, with the full expectation that the substituted product will produce equivalent clinical effects and safety profile as the original product.

HISTORY OF BIOEQUIVALENCE EVALUATION IN THE UNITED STATES

In 1938, the U.S. Congress enacted the Federal Food, Drug, and Cosmetic Act. The new law required, among other things, that a "new drug" product would need to provide proof of safety before it could be marketed. The New Drug Application (NDA) was established to provide a mechanism for proof of safety of drugs to be submitted to the FDA. Regulations were promulgated as to the form and content of the data to be submitted for an NDA. Originally, only toxicity studies were required along with informative labeling and adequate manufacturing data.

Drug Efficacy Study Implementation (DESI)

In 1962, The Kefauver–Harris Amendment to the Food, Drug, and Cosmetic Act required that all new drug products subsequently approved for marketing must have adequate evidence of effectiveness as well as safety.[1] The FDA was assigned the responsibility for receiving, reviewing, and evaluating required data submissions and enforcing compliance with the law. An applicant submitting an NDA was now required to submit "substantial evidence" in the form of "adequate and well-controlled studies" to demonstrate the effectiveness of the drug product under the conditions of use described in its labeling. The new drug effectiveness provision of the law also applied retrospectively to all drugs approved between 1938 and 1962 based on safety only. The FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to review this group of drugs for effectiveness. The NAS/NRC appointed 30 panels of experts and initiated the Drug Efficacy Study. The panels reviewed approximately 3400 drug formulations and classified them either effective or less than effective.[2] The FDA reviewed the reports and any supporting data and published its conclusions in the Federal Register as DESI notices. The DESI notices contained the acceptable marketing conditions for the class of drug products covered by this notice.

Many drug products had active ingredients and indications that were identical or very similar to those of drug products found to be effective in the DESI review but lacked NDAs themselves. Initially, in implementing the DESI program, the FDA required that each of these duplicate drug products should have its own approved NDA before it could be legally marketed. Later, the FDA concluded that a simpler and shorter drug application was adequate for approving duplicate DESI drugs for marketing and, in 1970, created the Abbreviated New Drug Application (ANDA) procedure for approving duplicate DESI drug products.[3–5] The FDA believed that it was not necessary for firms seeking approval of duplicate DESI drug products

to establish the safety and efficacy of each new product identical in active ingredient and dosage form with a drug product previously approved as safe and effective. However, many of the DESI notices included, as a requirement for approval of the duplicate drug application, presentation of evidence that the "biological availability" of the test product was similar to that of the innovator's product.

Development of the FDA's Bioavailability/Bioequivalence Regulations

Introduction in the late 1960s and early 1970s of sophisticated bioanalytical techniques made possible measurements of drugs and metabolites in biological fluids at concentrations as low as a few nanograms per milliliter. Because these techniques were applied to investigate the relative bioavailability of various marketed drug products, it became apparent that many generic formulations were more bioavailable than the innovator products, whereas others were less bioavailable.

In the late 1960s and early 1970s, many published studies documented differences in the bioavailability of chemically equivalent drug products, notably chloramphenicol,[6] tetracycline,[7] phenylbutazone,[8] and oxytetracycline.[9] In addition, a number of cases of therapeutic failure occurred in patients taking digoxin. These patients required unusually high maintenance doses and were subsequently found to have low plasma digoxin concentrations.[10] A crossover study conducted on four digoxin formulations available in the same hospital at the same time revealed striking differences in bioavailability. The peak plasma concentrations, after a single dose, varied by as much as sevenfold among the four formulations. These findings caused considerable concern because the margin of safety for digoxin is sufficiently narrow that serious toxicity or even lethality can result if the systemically available dose is as little as twice that needed to achieve the therapeutic effect.

Creation of an Office of Technology Assessment (OTA)

To address this problem of bioinequivalence among duplicate drug products, the U.S. Congress in 1974 created a special OTA to provide advice on scientific issues, among which was the bioequivalence of drug products. The OTA formed the Drug Bioequivalence Study Panel. The basic charge to the panel was to examine the relationships between chemical and therapeutic equivalence of drug products and to assess whether existing technological capability could assure that drug products with the same physical and chemical composition would produce comparable therapeutic effects. After an extensive investigation of the issues, the panel published its findings to the US Congress in a report, dated July 15, 1974, entitled Drug Bioequivalence.[11,12] The panel concluded that variations in drug bioavailability were responsible for some instances of therapeutic failures and that analytical methodology was available for conducting bioavailability studies in man. Several recommendations pertained to in vivo bioequivalence evaluation. The panel recommended that efforts should be made to identify classes of drugs for which evidence of bioequivalence is critical, that current law requiring manufacturers to make bioavailability information available to the FDA should be strengthened, and that additional research aimed at improving the assessment and prediction of bioequivalence was needed.

Publication of the 1977 Bioavailability and Bioequivalence Regulations

In 1977, the FDA published its *Bioavailability and Bioequivalence* regulations under Title 21 of the Code of Federal Regulations (21 CFR). The regulations were divided into Subpart A: *General Provisions*, Subpart B: *Procedures for Determining the Bioavailability of Drug Products*, and Subpart C: *Bioequivalence Requirements*.[13] With the publication of these regulations, a generic firm could file an ANDA that provided demonstration of bioequivalence to an approved drug product in lieu of clinical trials. Subpart B defined bioavailability in terms of rate and extent of drug absorption, described procedures for determining bioavailability of drug products, set forth requirements for submission of in vivo bioavailability data, and provided general guidelines for the conduct of in vivo bioavailability studies. Subpart C set forth requirements for marketing a drug product subject to a bioequivalence requirement. ANDAs were generally still restricted to duplicates of drug products approved before October 10, 1962 and determined to be effective for at least one indication in a DESI notice.

An important feature of the 1977 regulations was the provision for waiver of in vivo bioequivalence study requirements (biowaivers) under certain circumstances. Applicants could file biowaiver requests for oral dosage forms and oral solubilized dosage forms. Waivers could be granted duplicate DESI-effective immediate-release oral drug products with no known bioequivalence problems. Biowaivers could also be granted for drug products in the same dosage form, but a different strength, and proportionally similar in active and inactive ingredients to a drug product from the same manufacturer for which in vivo bioavailability had been demonstrated. Both drug products were required to meet an appropriate in vitro test (generally dissolution) approved by the FDA.

Availability of the Paper NDA Route for Duplicate Drug Products

The FDA did allow some duplicate drug versions of post-1962 drug products to be marketed under a "paper NDA" policy.[14] Under this policy, in lieu of conducting their own tests, manufacturers of such duplicate drug products could submit safety and effectiveness information derived primarily from published reports of well-controlled studies. However, such reports of adequate and well-controlled studies in the literature were limited, and the FDA staff effort involved in reviewing paper NDAs became a substantial and often inefficient use of resources.

1984 Hatch–Waxman Amendments

In 1984, the Drug Price Competition and Patent Term Restoration Act (the Hatch–Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act by creating Section 505(j) of the Act (21 USC 355(j)), which established the present ANDA approval process.[15] Section 505(j) extended the ANDA process to duplicate versions of post-1962 drugs but also required that an ANDA for any new generic drug product shall contain information to show that the generic product is bioequivalent to the reference listed drug product. Evidence of bioequivalence was now required for all dosage forms.

1992 Revisions to the FDA's Bioavailability/Bioequivalence Regulations

In 1992, the FDA revised the *Bioavailability and Bioequivalence Requirements* of 21 CFR Part 320 to implement the Hatch–Waxman Amendments.[16] In its present form, 21 CFR Part 320 consists of Subpart A: *General Provisions* and Subpart B: *Procedures for Determining the Bioavailability and Bioequivalence of Drug Products.* Subpart A describes general provisions including definitions of bioavailability and bioequivalence. Subpart B states the basis for demonstrating in vivo bioavailability or bioequivalence and lists types of evidence to establish bioavailability or bioequivalence, in descending order of accuracy, sensitivity, and reproducibility. Subpart B also provides guidelines for the conduct and design of an in vivo bioavailability study and lists criteria for waiving evidence of in vivo bioequivalence.

As per the FDA's current *Bioavailability and Bioequivalence* regulations, statistical evaluation of bioequivalence studies of systemically active drugs is based on the analysis of drug concentrations in blood or plasma/serum. The rate of drug absorption is based on peak drug concentrations (C_{max}). The extent of drug absorption is based on the area under the drug concentration versus time profile (AUC). Generally, both AUC determined until the last measurable sampling time (AUC_{0-t}) and AUC extrapolated to infinity (AUC_{∞}) are evaluated.

Early Days of the FDA's Bioequivalence Review Process

Criteria for approval of generic drugs have evolved since the 1970s.[17] In the early 1970s, approval was based on mean data. Mean AUC and C_{max} values for the generic product had to be within ±20% of those of the brand-name product. In addition, plasma concentration-time profiles for immediate-release products had to be reasonably superimposable. Beginning in the late 1970s, the 75/75 (or 75/75–125) rule was added to the criteria. According to the 75/75 rule, the test/reference ratios of AUC and C_{max} had to be within 0.75 to 1.25 for at least 75% of the subjects. This was an attempt to consider individual variability in rate and extent of absorption. In the early 1980s, the power approach was applied to AUC and C_{max} parameters in conjunction with the 75/75 rule. The power approach consisted of two statistical tests: (1) a test of the null hypothesis of no difference between formulations using the F test and (2) the evaluation of the power of a test to detect a 20% mean difference in treatments.

Statistically, the power approach and the 75/75 rule have poor performance, and the FDA discontinued the use of these methods in 1986. The problems with both the 75/75 rule and power approach methods arose from the fact that they were based on the conventional null hypothesis test of no difference. Conventional hypothesis testing does not assess the evidence in favor of the conclusion that the test and reference means are equivalent but rather assesses the evidence in favor of a conclusion that the test and reference means are different, which is not the question of interest in bioequivalence analysis.[18–20] That is, the objective of bioequivalence analysis is to establish whether the test and reference means are equivalent—in other words, is the difference between the two means an acceptable difference?

TWO ONE-SIDED TESTS PROCEDURE FOR ANALYZING BIOEQUIVALENCE DATA

The two one-sided tests procedure, used by the FDA since 1986 for bioequivalence analysis, resolved the problems of hypothesis testing.[20] The two one-sided tests procedure tests two conditions. Stated simply, the first condition tests if the test product is significantly less bioavailable than the reference product. The second condition tests if the reference product is significantly less bioavailable than the test product. A significant difference is defined as 20% at $\alpha = 0.05$. The criteria above may be restated to illustrate the rationale for the 0.80 to 1.25 (or 80%–125%) confidence interval (CI) criteria. In the first test, the bioequivalence limit for the test/reference ratio is 0.80. In the second test, the bioequivalence limit for the reference/test ratio is 0.80. Because, by convention, bioequivalence ratios are expressed as test/reference, the second bioequivalence limit is 1.25, that is, the reciprocal of 0.80. This may be stated in clinical terms as follows. If a patient is currently receiving a brand-name reference product and is switched to a generic product, the generic product should not deliver significantly less drug to the patient than the brand-name product. Conversely, if a patient is currently receiving the generic product and is switched to the brand-name reference product, the brand-name product should not deliver significantly less drug to the patient than the generic product. Computationally, the two one-sided tests procedure as described above (with each of the two tests conducted at an $\alpha = 0.05$) yields exactly the same results as an analysis of variance (ANOVA) conducted at the 90% level. This ANOVA procedure is much easier to conduct using standard statistical analysis software.

Logarithmic Transformation of Bioequivalence Data

Until 1992, the FDA generally recommended that applicants perform ANOVA on untransformed AUC and C_{max} data to determine the 90% confidence limits of the differences. After a 1991 meeting of the Generic Drugs Advisory Committee, which focused on statistical analysis of bioequivalence data, the FDA began to recommend that applicants perform ANOVA on log-transformed data.

The Generic Drug Advisory Committee recommended log transformation for bioequivalence analysis for two reasons. First, the ANOVA used to conduct the bioequivalence statistics is based on a linear statistical model.[21,22] However, the form of expression for AUC suggests a multiplicative model, because $AUC = (F * D)/(V * Ke)$, where F is the fraction of drug absorbed, D is the dose, V is the volume of distribution, and Ke is the elimination rate constant. For this reason, FDA statisticians concluded that effects on AUC are not additive if the data are analyzed on the original scale of measurement. Thus, because $\ln(AUC)$ is equal to $\ln(F) + \ln(D) - \ln(V) - \ln(Ke)$, logarithmic transformation of AUC allows it to be analyzed using the ANOVA, which assumes a linear statistical model. A similar argument can be made for C_{max}.

The second reason for log transformation is that C_{max} and AUC, like much biological data, correspond more closely to a log-normal distribution than to a normal distribution.[23] Plasma concentration data and derived pharmacokinetic parameters

tend to be skewed, and their variances tend to increase with the means. Log transformation generally remedies this situation and makes the variances independent of the means. In addition, skewed frequency distributions are often made more symmetrical by log transformation.

To summarize, since 1992, the FDA expects applicants to perform ANOVA on the geometric mean test/reference AUC and C_{max} ratios.[23] To obtain geometric means, the data are log transformed before conducting an ANOVA and then back-transformed before calculating the test/reference ratios. Each of the two one-sided tests is carried out at the $\alpha = 0.05$ (5%) level. The 90% CIs of the geometric mean test/reference ratios should fall within 0.8 to 1.25 (80%–125%). The determination of bioequivalence using this approach is termed "average bioequivalence."[20]

REFERENCE-SCALED AVERAGE BIOEQUIVALENCE APPROACH

For drugs with an expected within-subject variability of 30% or greater, the FDA recommends using a reference-scaled average bioequivalence approach.[24,25] Either a three- or a four-period study design can be used, provided that the same lot of the reference product is administered twice to determine its within-subject variability (s^2_{WR}). The test product variability is not used in the bioequivalence statistical calculations. The minimum number of subjects that would be acceptable is 24.

Scaled average bioequivalence for both AUC and C_{max} is evaluated by testing the following null hypothesis:

$$H_0 : \frac{(\mu_T - \mu_R)^2}{\sigma^2_{WR}} > \theta, \tag{10.1}$$

(for given $\theta > 0$) versus the alternative hypothesis

$$H_1 : \frac{(\mu_T - \mu_R)^2}{\sigma^2_{WR}} \leq \theta, \tag{10.2}$$

where μ_T and μ_R are the averages of the log-transformed measures C_{max} and AUC for the test and reference products, respectively; σ^2_{WR} is the reference product within-subject variability; and θ is the scaled average bioequivalence limit. Usually, testing is done at level $\alpha = 0.05$. Furthermore,

$$\theta = \frac{(\ln \Delta)^2}{\sigma^2_{W0}}, \tag{10.3}$$

where Δ is 1.25, the usual average bioequivalence upper limit for the untransformed test/reference ratio of geometric means, and σ_{W0} is a regulatory constant set at a value of 0.25 by the FDA. The regulatory constant rejection of the null hypothesis H_0 supports the conclusion of equivalence.

Thus, in a study that uses the reference-scaled average bioequivalence approach, the 95% upper confidence bound for $\frac{\left(\bar{Y}_T - \bar{Y}_R\right)^2}{s_{WR}^2}$ must be ≤θ, where $\bar{Y}_T$ and $\bar{Y}_R$ are the means of the log-transformed bioequivalence measures AUC and/or C_{max} for the test and reference products, respectively, and s_{WR}^2 is the within-subject variance of the reference product bioequivalence measure determined in the study, and the scaled average bioequivalence limit $\theta \equiv \left(\frac{\ln(1.25)}{\sigma_{W0}}\right)^2$. Equivalently, a 95% upper confidence bound for $\left(\bar{Y}_T - \bar{Y}_R\right)^2 - \theta s_{WR}^2$ must be ≤0.

The scaling is mixed due to the presence of the regulatory constant σ_{W0} in the scaling model. The regulatory constant, which is set at 0.25 by the FDA, is the degree of variability at which the CI limits begin to widen. Figure 10.1 graphically illustrates how bioequivalence limits are determined with mixed scaling. Although, using the above equations, bioequivalence limits begin to widen at a σ_{W0} of 0.25, FDA sets the additional criterion that the within-subject standard deviation of the reference product (s_{WR}) must be at least 0.294 before scaling of the bioequivalence acceptance criteria is actually applied to the data. The use of this cutoff provides additional assurance that the consumer risk or type I error rate of 0.05 will be maintained. Finally, the point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25].

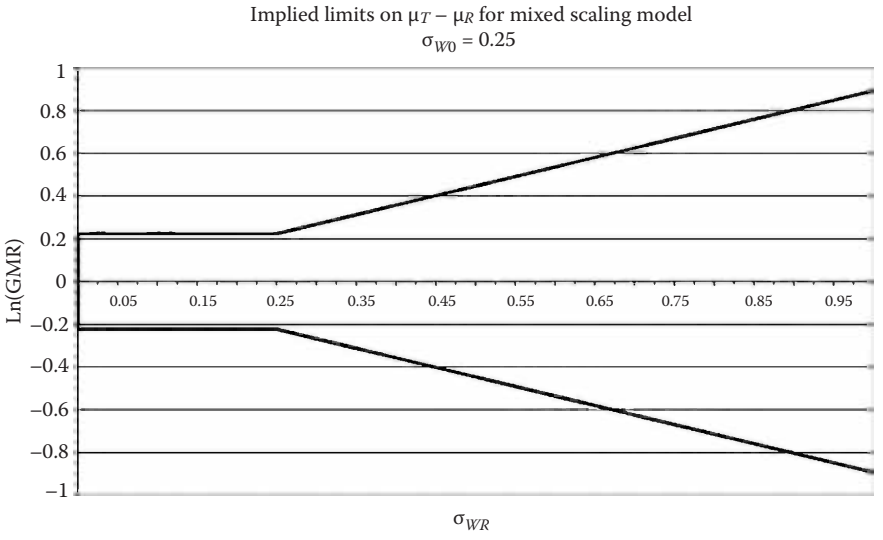

FIGURE 10.1 Implied bioequivalence limits are plotted as a function of the population reference product within-subject variability of the bioequivalence measure (C_{max} or AUC). When $\sigma_{W0} \leq 0.25$, for an acceptable bioequivalence study, the 90% CI of the bioequivalence measure test/reference geometric mean ratios must fall within 80% to 125% limits. When $\sigma_{W0} > 0.25$, the implied bioequivalence limits scale as reference product within-subject variability increases. The slope of this portion of the curve is determined by the value of σ_{W0}.

ROLE OF T_{max} IN BIOEQUIVALENCE ANALYSIS

The FDA does not ask ANDA applicants to use statistical procedures to compare the time to drug peak plasma concentrations (T_{max}) for the test and reference products.[26] Although theoretically a relatively sensitive measure of absorption rate, T_{max} is thought to have shortcomings as an indirect measure of the rate of drug absorption.[27,28] For example, ANOVA analysis cannot be applied to T_{max}, because T_{max} is a discrete measure dependent on frequency of blood sampling.[29] In addition, most pharmacokinetic studies typically employ irregular sampling schemes to collect T_{max} data, and as a result, these data are not routinely amenable to proper statistical evaluation.[30] Nonetheless, the FDA believes that T_{max} should be considered in bioequivalence decision-making and routinely examines T_{max} data in bioequivalence studies as supportive data to verify that the test and reference products have the same rate of absorption.[31]

PARTIAL AUC

In certain circumstances, the FDA recognizes that it is appropriate to use a partial AUC (pAUC) as an exposure metric to ensure that a generic and reference product have comparable therapeutic benefit.[32,33] The pAUC is an exposure metric determined by truncating the area under the plasma concentration versus time profile at a designated early time after dosing. The choice of truncation time is most appropriately based on the pharmacokinetic/pharmacodynamic or efficacy/safety data for the drug under examination.[34]

The FDA requests inclusion of pAUC metrics in bioequivalence studies of generic versions of multiphasic modified-release reference formulations designed to produce rapid drug action followed by a sustained effect. The desired outcome of rapid early response followed by sustained response is achieved by formulating the reference product as a combination of immediate-, delayed-, and/or extended-release components.[33] An additional criterion that must be satisfied to appropriately apply pAUC metrics is that the drug does not accumulate to steady-state under the multiphasic product's recommended dosing regimen.

For such products, the FDA recommends use of both an early pAUC measure to compare drug exposure responsible for early onset of response, and a late pAUC to compare drug exposure associated with the second sustained release of drug. These two metrics replace AUC_{0-t} in bioequivalence evaluation. Thus, the metrics used are AUC_{0-T} (where T is the early sampling truncation time), AUC_{T-t} (where t is the time of the last measurable plasma drug concentration), C_{max}, and AUC_{∞}. It is not necessary for the generic version to contain the same ratios of immediate- and delayed- or extended-release components as the multiphasic modified-release reference. A generic version is considered therapeutically equivalent to a corresponding multiphasic modified-release reference drug product if the two are shown to be bioequivalent based on the parameters AUC_{0-T}, AUC_{T-t}, AUC_{∞}, and C_{max}.

Figure 10.2 illustrates the application of the pAUC and other bioequivalence metrics in the case where a multiphasic reference product is formulated to release drug in such a manner as to achieve an early onset of response followed by a sustained

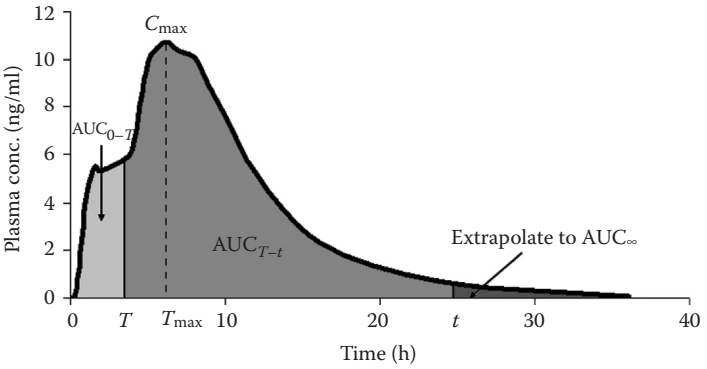

FIGURE 10.2 pAUC refers to the AUC between two specified, clinically relevant, time points on the drug plasma concentration versus time profile. pAUC metrics should meet bioequivalence limits for generic versions of multiphasic modified-release oral dosage formulations, which are formulated both to rapidly release drug from an immediate-release portion to achieve rapid onset of response and to slowly release drug from a delayed- or extended-release portion to sustain the response. An additional criterion for using the pAUC metric for such formulations is that the drug should not accumulate when administered under the appropriate dosing regimen. The geometric mean test/reference ratios of the four metrics C_{max}, AUC_{0-T}, AUC_{T-t}, and AUC_∞ should fall within the limits of 80% to 125%. The metric C_{max} is the peak plasma drug concentration. The sampling time for the pAUC determination (T) is selected based on the pharmacokinetic/pharmacodynamic properties of the active ingredient. The first pAUC, AUC_{0-T}, compares test and reference systemic exposure responsible for early onset of the therapeutic response. The second pAUC, AUC_{T-t}, where t is the last sampling time point with measurable drug concentration, compares test and reference systemic exposure responsible for sustaining the therapeutic response. The metric AUC_∞ is the AUC extrapolated to infinity, representing total drug systemic exposure after a single dose.

response. To date, the FDA includes the pAUC in bioequivalence evaluation of multiphasic modified-release formulations of zolpidem,[35,36] methylphenidate,[37] dexmethylphenidate,[38] and mixed amphetamines.[39] These four products meet the criteria described above for pAUC application. For these four products, the FDA scientists selected the pAUC truncation times based on the relationship between drug plasma pharmacokinetic profiles and the time course of the associated pharmacodynamic response.

GENERAL BIOEQUIVALENCE STUDY DESIGN RECOMMENDATIONS

There are several types of designs suitable for in vivo bioequivalence studies. The preferred design for most orally administered dosage forms is a two-way crossover, two-period, two-sequence, single-dose study, in healthy subjects, performed under fasting conditions. Each study subject receives each treatment, test and reference, in random order. Plasma or blood samples are collected for three or more pharmacokinetic half-lives for determination of the rate and extent of drug release from the dosage form and absorption by each subject. A washout period is scheduled between

the two periods to allow the subjects to completely eliminate the drug absorbed from the first dose before administration of the second dose. Also, for long half-life drugs, a single-dose parallel design may be used.[40] For drugs that demonstrate low intrasubject variability in distribution and clearance, an AUC truncated at 72 hours may be used in place of AUC_{0-t} or AUC_{∞}.[26]

Number of Subjects; Single-Dose versus Steady-State Bioequivalence Studies

The FDA recommends that investigators enroll a minimum of 12 subjects.[25] Most bioequivalence studies submitted in support of ANDAs enroll from 24 to 36 subjects. The FDA asks investigators to conduct single-dose bioequivalence studies because it has been shown that these are more sensitive to detecting differences in formulation performance than multiple-dose studies.[26,41–45]

Appropriate Drug Product Strength for Bioequivalence Studies

Most bioequivalence studies are conducted on the highest strength of a drug product line, unless it is necessary to use a lower strength for safety reasons. Use of the highest strength is particularly critical for drugs that display nonlinear kinetics because of nonlinear (usually capacity-limited) elimination or presystemic metabolism, with the result that plasma concentrations increase more than proportionally with an increase in dose.[46] For such drugs, small differences in the rate or extent of absorption can potentially have substantial effects on the AUC.[47] Thus, using the highest strength in bioequivalence studies or, in some cases, the highest starting dose—so that drug pharmacokinetics are potentially in the "nonlinear range"—ensures that a generic formulation will not pass bioequivalence acceptance criteria unless it is formulated to provide nearly the same rate and extent of exposure as the corresponding reference product. For drugs for which rate and/or extent of absorption increases less than proportionally with an increase in dose,[48] the bioequivalence study will be most discriminating if conducted at the lowest strength or, if only one strength is marketed, at the lowest recommended dose.

Fed Bioequivalence Studies

Because food can influence the bioavailability of orally administered drugs, the FDA recommends that applicants conduct bioequivalence studies under fed conditions in most cases. The FDA's Guidance for Industry, *Food-Effect Studies and Fed Bioequivalence Studies* ("Food Guidance"), contains recommendations about designing fed bioequivalence studies.[49] Fed bioequivalence studies are generally conducted using meal conditions expected to provide the greatest effects on formulation performance and gastrointestinal physiology such that systemic drug bioavailability may be maximally affected. Typically, the drug is administered to subjects within 30 minutes of consuming a high-fat, high-calorie meal. The FDA recommends that these studies use a randomized, balanced, single-dose, two-treatment (fed test vs. fed reference), two-period, two-sequence crossover design. The acceptance criteria for fed bioequivalence studies is the same as for fasting bioequivalence studies—the

90% CI of the geometric mean test/reference AUC and C_{max} ratios must fall within the limits of 80% to 125%.

The FDA presently requests fed bioequivalence studies for all immediate- and modified-release oral dosage forms, with few exceptions. Generally, if the labeling warns that the product should be taken only on an empty stomach for reasons of safety or efficacy, then fed bioequivalence studies are not recommended; in such cases, it is necessary to evaluate bioequivalence only under fasting conditions.[50–52] In very few cases, bioequivalence is evaluated only under fed conditions because there are safety concerns associated with administration of the product on an empty stomach.[53]

Study Population in Bioequivalence Studies

The FDA recommends that in vivo bioequivalence studies be conducted in individuals that are representative of the general population, taking into account age, sex, and race factors.[26] For example, if a drug product is to be used in both sexes, the sponsor should attempt to include similar proportions of males and females in the study; if the drug product is to be used predominantly in the elderly, the applicant should attempt to include as many subjects of 60 years of age or older as possible. Restrictions on admission into the study should generally be based solely on safety considerations.

Bioequivalence studies should be conducted in the intended patient population when there are significant safety concerns associated with use in healthy subjects. For example, bioequivalence studies of drugs used for cancer chemotherapy are generally conducted in cancer patients.[54,55] These studies should be conducted in patients who are already stabilized on the medication of interest.

TYPES OF EVIDENCE TO ESTABLISH BIOAVAILABILITY AND BIOEQUIVALENCE

Subpart B of the *Bioavailability and Bioequivalence Requirements* in 21 CFR Part 320 lists the following in vivo and in vitro approaches to determining bioequivalence in descending order of accuracy, sensitivity, and reproducibility:[32]

- In vivo measurement of active moiety or moieties in biological fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

Bioequivalence Studies with Pharmacokinetic Endpoints

Figure 10.3 illustrates, for a model of oral dosage form performance, why the most sensitive approach is to measure the drug in biological fluids, such as blood, plasma, or serum. The active ingredient leaves the solid dosage form and dissolves in the

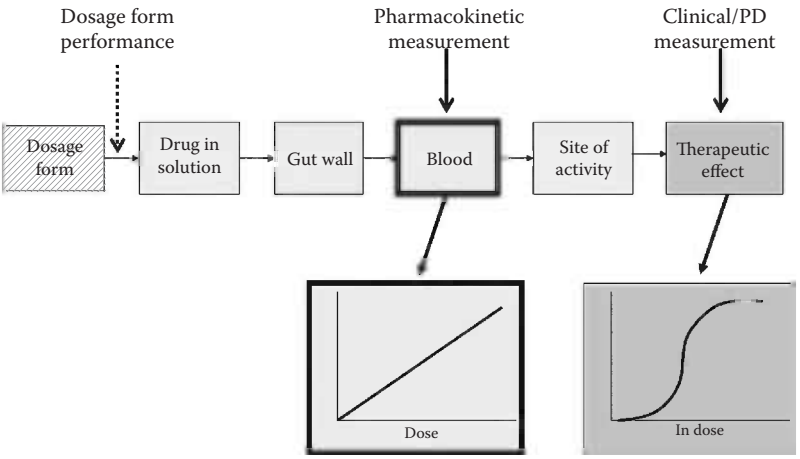

FIGURE 10.3 The most sensitive approach in evaluating bioequivalence of two formulations is to measure drug concentration in biological fluids, as illustrated in this diagram showing the relationship between dosage form performance and therapeutic response. After oral dosing, the active ingredient leaves the solid dosage form, dissolves in the gastrointestinal tract, and, after absorption through the gut wall, appears in the systemic circulation. Formulation performance is the major factor determining the critical steps of dosage form disintegration and drug substance dissolution before absorption. All other steps after in vivo drug substance dissolution are patient- or subject-determined processes not directly related to formulation performance. The variability of the measured endpoint increases with each additional step in the process, such that variability of clinical measures is quite high compared with that of blood concentration measures. As a result, a pharmacodynamic or clinical approach is not as accurate, sensitive, and reproducible as an approach based on plasma concentrations.

gastrointestinal tract and, after absorption through the gut wall, appears in the systemic circulation. The step involving release of drug substance from the dosage form and dissolution before absorption is the critical step that is determined by the formulation. Other steps illustrated in the diagram are patient- or subject-determined processes not directly related to formulation performance. Variability of the measured endpoint increases with each additional step in the process. Therefore, variability of clinical measures is usually quite high compared with blood concentration measures. Figure 10.4 shows that the blood concentration of a drug directly reflects the amount of drug delivered from the dosage form.

Most bioequivalence studies submitted to the FDA are based on measuring drug concentrations in plasma. In certain cases, whole blood or serum may be more appropriate for analysis. Measurement of only the parent drug released from the dosage form, rather than a metabolite, is generally recommended because the concentration-time profile of the parent drug is more sensitive to formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination.[26] If parent drug concentrations are too low to allow reliable measurement with modern assay methods, then bioequivalence statistics are performed on a

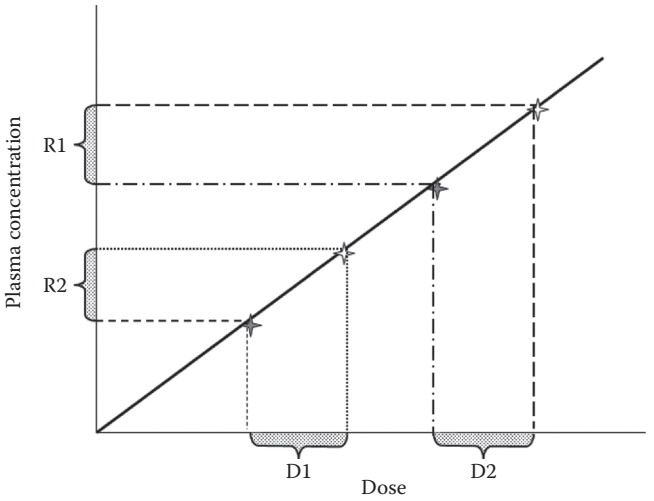

FIGURE 10.4 Blood concentration of a drug directly reflects the amount of drug delivered from the dosage form. The corresponding responses over a wide range of doses will be of adequate sensitivity to detect differences in bioavailability between two formulations. This is illustrated for two widely different doses, D1 and D2. Any differences in dosage form performance are reflected directly by changes in blood concentration (R1 and R2).

metabolite. Otherwise, if a metabolite is formed by presystemic or first-pass metabolism and contributes meaningfully to safety and efficacy, then FDA asks that metabolite plasma concentrations be measured and used to provide supportive evidence of comparable therapeutic outcome.

Urine measurements are not as sensitive as plasma measurements but are necessary for some drugs such as orally administered potassium chloride,[56] because serum concentrations are too low to allow for accurate measurement of drug absorbed from the dosage form. Both the cumulative amount of drug excreted (*Ae*) and the maximum rate of urinary excretion (R_{max}) are evaluated statistically in bioequivalence studies that rely on urine concentrations.

Bioequivalence Studies with Pharmacodynamic Endpoints

In situations where a drug cannot be reliably measured in blood, it may be appropriate to base bioequivalence evaluation on an in vivo test in humans in which an acute pharmacologic (pharmacodynamic) effect is measured as a function of time. The FDA accepts bioequivalence studies with pharmacodynamic endpoints for locally acting drug products. The pharmacodynamic response selected should directly reflect dosage form performance but may not necessarily directly reflect therapeutic efficacy. To be adequately sensitive to distinguish between two products that are not bioequivalent, the dose used in the pivotal bioequivalence study should be on the linear portion of the dose-response curve (Figure 10.5). A pilot pharmacodynamic study using the reference product can be conducted to determine the optimal dose for the pivotal bioequivalence study.

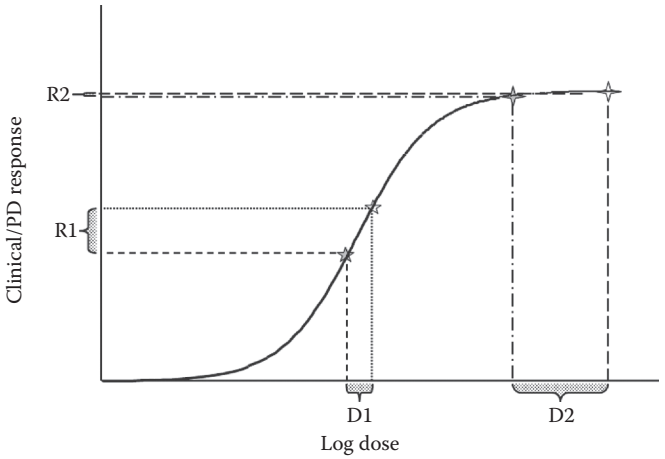

FIGURE 10.5 In evaluating bioequivalence in a study with pharmacodynamic or clinical endpoints, it is critical to select a dose that falls on the middle ascending portion of the sigmoidal dose-response curve. The most appropriate dose for a study based on pharmacodynamic or clinical endpoints should be in the range that produces a change in response (R1), as shown in the midportion of the curve (D1). A dose that is too high will produce a minimal response at the plateau phase of the dose-response curve, such that even large differences in dose (D2) will show little or no change in pharmacodynamic or clinical effect (R2). Thus, two formulations that are quite different may appear to be bioequivalent.

Orlistat is a minimally absorbed drug for which a pharmacodynamic endpoint study is suitable. As orlistat prevents the absorption of dietary fat by inhibiting lipases in the lumen of the gastrointestinal tract, a suitable pharmacodynamic endpoint is fecal fat excretion.[57,58] Three doses of the reference product are used to construct a dose-response curve and an E_{max} model is fit to the data. Two products are deemed bioequivalent if the 90% CI of the ratio of test and reference doses that produce an equivalent pharmacodynamic response falls within 80% to 125%. Acarbose is another minimally absorbed oral drug product for which bioequivalence can be determined using a pharmacodynamic approach.[59] Acarbose lowers blood glucose by inhibiting the activity of α-glucosidase within the gastrointestinal tract. In this case, the pharmacodynamic endpoint is based on the ability of acarbose to lower serum glucose after administration of a sucrose load. To establish acarbose bioequivalence, the 90% CIs for the test/reference ratios for the area under the effect curve and C_{max} should fall within 80% to 125%.[60]

Bioequivalence Studies with Clinical Endpoints

For some products, the most appropriate bioequivalence approach is to conduct a well-controlled trial with clinical endpoints. A clinical endpoint study is conducted in patients and is based on evaluation of a therapeutic response. The clinical response follows a similar dose-response pattern to the pharmacodynamic response, as shown in Figure 10.5. Thus, in designing bioequivalence studies with clinical endpoints, the

same considerations for dose selection apply as for pharmacodynamic endpoints. The appropriate dose for a clinical endpoint bioequivalence study should be on the linear portion of the dose-response curve, because a response in this range will be the most sensitive to changes in formulation performance. Due to high variability and the subjective nature of many clinical evaluations, the clinical approach is the least accurate, sensitive, and reproducible of the in vivo approaches to determine bioequivalence.

Two examples of orally administered, minimally absorbed products for which clinical endpoint bioequivalence studies are suitable are lubiprostone, indicated for the treatment of chronic idiopathic constipation in adults,[61] and rifaximin, indicated for traveler's diarrhea caused by noninvasive *Escherichia coli* infections.[62] For lubiprostone capsules, the appropriate patient population is male and female subjects with chronic idiopathic constipation, and the recommended endpoint is the mean change from baseline in the number of spontaneous bowel movements during Week One.[63] As mean change from baseline is a continuous variable, to establish bioequivalence, the 90% CI for the test/reference ratios of means must be contained within [0.8, 1.25]. For rifaximin tablets, the appropriate patient population is male and female subjects with traveler's diarrhea, and the recommended endpoint is clinical cure (no watery stools or no more than two soft stools within a 24-hour period with no fever and no other enteric symptoms).[64] As the success versus failure endpoint is dichotomous, to establish bioequivalence, the 90% CI of the test/reference difference between products for the primary endpoint must be contained within [–0.2, +0.2]. Both lubiprostone and rifaximin should be statistically superior to placebo ($P < 0.05$, two-sided) for the respective primary endpoints to assure that each drug product is actually producing a clinical effect. If the products are not producing an effect greater than placebo, then the study is not sensitive to a difference in the test versus reference products.

Bioequivalence Studies with In Vitro Endpoints

Bioequivalence may be established by in vitro studies alone,[65] for some locally acting oral dosage forms. Two types of in vitro endpoints are generally used in such cases.

The first type of in vitro endpoint is binding, illustrated by approaches for the locally acting resins cholestyramine[66] and sevelamer.[67] These two products produce their corresponding therapeutic effects by forming nonabsorbable complexes in the intestine with bile acids and phosphate salts, respectively. Thus, the in vitro measures of bioequivalence are based on binding rates, which reflect the underlying mechanism of action, and as such are directly related to the rate and extent of drug availability. The 90% CI of the test/reference ratios of the equilibrium binding constants should fall within 0.80 to 1.25.

The second type of in vitro endpoint is dissolution. This approach is recommended for locally acting low permeability oral dosage forms that are highly soluble, dissolve relatively rapidly, and are formulated to be qualitatively and quantitatively (Q1/Q2) the same as the corresponding reference products. The rationale for this approach is that (1) low permeability will ensure minimal loss of bioavailability due to absorption, (2) rate and extent of drug release to the site of action will be affected by the rate of in vitro dissolution, and (3) high solubility and relatively rapid dissolution will ensure that the product will form a solution and stay in solution before

reaching the site of action in the intestine.[59] Thus, once dissolved, local distribution of the drug will be the same for a generic and corresponding reference. If two products are Q1/Q2, the only possible difference affecting bioavailability at the site of action in the gastrointestinal tract will be the rate of dissolution. This approach has been used for Q1/Q2 acarbose tablets (as an alternative to the pharmacodynamic approach described above) and for Q1/Q2 vancomycin capsules. Test and reference dissolution profiles must not differ significantly in media of pH 1.2, 4.5, and 6.8; the F2 metric (similarity factor) is used for these comparisons.[68]

WAIVERS OF IN VIVO BIOEQUIVALENCE TESTING REQUIREMENTS FOR ORAL DOSAGE FORMS

Biowaivers can be granted for oral solution drug products, provided that the generic formulation does not contain an excipient that can significantly affect absorption.[69] It is not necessary for a generic oral solution formulation to be Q1/Q2 the same as the corresponding reference formulation. Biowaivers can still be granted for DESI drug immediate-release formulations with no bioequivalence problems,[69] provided that in vitro dissolution is acceptable.

Biowaivers can be granted for one or more lower strengths of an immediate-release product line based on acceptable dissolution testing and acceptable in vivo bioequivalence on the highest strength.[26] All strengths should be proportionally similar in active and inactive ingredients. For reasons of safety, it may be necessary to conduct the in vivo study on a strength that is not the highest. In these cases, the FDA will consider a biowaiver request for a higher strength if elimination kinetics are linear over the dose range, if the strengths are proportionally similar, and if comparative dissolution testing on all strengths is acceptable.[70,71]

Modified-Release Drug Products

For modified-release oral drug products, the process of determining whether lower strengths are bioequivalent to the corresponding reference product strengths varies depending on whether the product is a capsule or tablet.[72] For capsules in which the strength differs only in the number of identical beads containing the active moiety, it is not necessary for the applicant to conduct in vivo testing on lower strengths provided that dissolution testing is acceptable and that bioequivalence is demonstrated in an in vivo study for the highest strength. For tablets, it may not be necessary to conduct in vivo studies on lower strengths provided that (1) the lower strengths are proportionally similar in its active and inactive ingredients to the strength that underwent acceptable in vivo bioequivalence testing and (2) the dissolution profiles of the lower strengths in at least three media (e.g., pH 1.2, 4.5, and 6.8) are similar to the profiles of the strength that underwent acceptable in vivo testing.

Biopharmaceutics Classification System

Applicants can request biowaivers for immediate-release products based on an approach termed the biopharmaceutics classification system (BCS).[73] The BCS is a

framework for classifying drug substances based on solubility and intestinal permeability. With product dissolution, these are the three major factors governing rate and extent of absorption from immediate-release products. The BCS classifies drug substances as follows:

- Class 1: high solubility, high permeability
- Class 2: low solubility, high permeability
- Class 3: high solubility, low permeability
- Class 4: low solubility, low permeability

The FDA believes that demonstration of in vivo bioequivalence may not be necessary for immediate-release products containing BCS Class 1 drug substances, as long as the inactive ingredients do not significantly affect absorption of the active ingredient(s). This is because, when a drug dissolves rapidly from the dosage form (in relation to gastric emptying) and has high intestinal permeability, the rate and extent of its absorption is likely to depend on dissolution and/or gastrointestinal transit time.

The CDER Guidance for Industry: *Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*[73] recommends methods for determining drug solubility and permeability for applicants who wish to request biowaivers based on BCS. The drug solubility class boundary is based on the highest dose strength of the product that is the subject of the biowaiver request. The permeability class can be determined in vivo (mass balance, absolute bioavailability, or intestinal perfusion approaches) or in vitro (permeation studies using excised tissues or a monolayer of cultured epithelial cells). Test and reference dissolution profiles should be compared in three media: 0.1 N HCl or simulated gastric fluid without enzymes, pH 4.5 buffer, and pH 6.8 buffer or simulated intestinal fluid without enzymes.

FAILED BIOEQUIVALENCE STUDIES

Figure 10.6 shows scenarios of acceptable and failed bioequivalence results for several hypothetical formulations. As the width of the 90% CI in the bioequivalence study is controlled by the number of subjects and by the variability of the pharmacokinetic measures, many bioequivalence studies fail due to underpowering, for various reasons. The applicant may have failed to enroll an adequate number of subjects. There may be an excessive number of withdrawals, or there may be missing data because of lost samples. Sometimes a study may fail because of subjects who appear to have an aberrant response on a given dosing day.[74] For example, noncompliant subjects may cause the study to fail. The FDA discourages deletion of outlier values, particularly for nonreplicated study designs.[23]

"All Bioequivalence Studies" Rule for Generic Drug Submissions

In 2009, the FDA published a new final rule relating to failed or additional bioequivalence studies, "Requirements for Submission of Bioequivalence Data."[75] The new

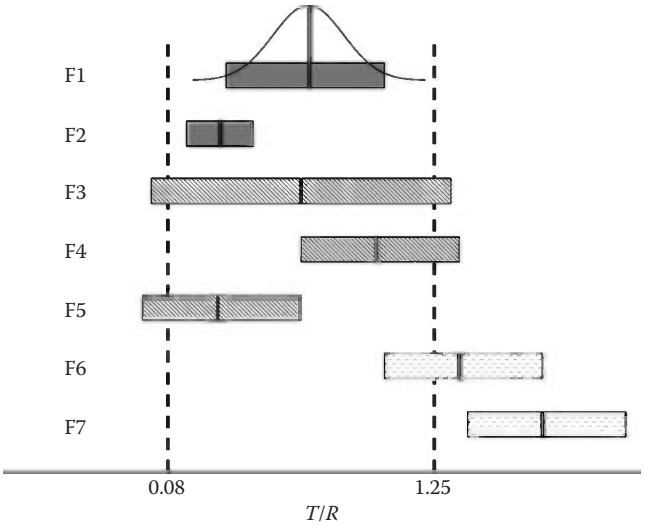

FIGURE 10.6 Hypothetical bioequivalence study results for formulations F1 to F7 illustrate various scenarios of passing and failing bioequivalence criteria. The width of each 90% CI is shown as a bar, although, in actuality, the log-transformed test/reference (*T/R*) ratios are distributed as a bell-shaped curve. F1 and F2 represent results of studies in which the 90% CIs of the *T/R* ratios fall between 0.80 and 1.25 (pass bioequivalence criteria). For F1, the ratio of *T/R* means (point estimate) is near 1.00. For F2, the point estimate is less than 1.00, but, because of low variability, the 90% CI of *T/R* ratios still falls within acceptable limits. F3 to F7 show ways in which studies fail to pass CI criteria. With F3, the point estimate is near 1.00, but, because of high variability, the 90% CI is very wide and the drug does not pass bioequivalence criteria. F3 may pass CI criteria if the number of study subjects is increased. By contrast, F4 to F7 have variability comparable with F1. F4 represents a failure on the low side (*T* is less bioavailable than *R*), and F5 represents a failure on the high side (*R* is less bioavailable than *T*). Because the point estimates for F3 and F4 are still within the 0.8 to 1.25 range, these formulations may also meet CI criteria if a greater number of subjects are dosed. F6 does not meet the upper bound of the 90% CI, and the point estimate exceeds 1.25. For F7, the entire CI is outside the acceptance criteria (bioinequivalence). Formulations F6 and F7 are so different from the reference that both will still fail CI criteria even if the number of subjects is increased.

rule amended 21 CFR Parts 314 and 320 to require an ANDA applicant to submit data from all bioequivalence studies that an applicant conducts on a drug product formulation submitted for approval, including studies that do not meet the specified bioequivalence criteria. These data must be submitted as either a complete study report or a summary report of the bioequivalence data. The term "same drug product formulation" means the formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval but are similar enough to be relevant to the Agency's determination of bioequivalence. FDA Guidance for Industry, *Submission of Summary Bioequivalence Data for ANDAs*, provides information on the types of ANDA submissions covered by the final rule, a recommended format for

summary reports of bioequivalence studies, and the types of formulations that FDA considers to be the same drug product formulation for different dosage forms based on differences in composition.[76]

CONCLUSION

It should be clear that regulatory bioequivalence evaluation of generic drug products is quite rigorous. In fact, surveys of bioequivalence data in ANDAs approved since the enactment of the Hatch–Waxman Amendments in 1984 show that the rate and extent of drug exposure from generic drugs differ very little from that of their corresponding innovator counterparts.[77–79] Based on many years of experience and thousands of approved products evaluated using the rigorous approaches described in this chapter, the FDA believes an approved generic product can be substituted for the brand product with assurance that the two products will produce equivalent therapeutic effects in each patient.

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11 Statistical Considerations for Establishing Bioequivalence

*Charles Bon and Sanford Bolton**

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INTRODUCTION

The assessment of "bioequivalence" (BE) refers to a procedure that compares the bioavailability of a drug from different formulations. Bioavailability is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action. In this chapter, we will not present methods for drugs that are not absorbed into the bloodstream (or absorbed so little as to be unmeasurable) or where the concentration-time profile of the drug in the bloodstream is not considered to reflect the rate and extent of the drug at the site of action (e.g., topically active products). However, statistical methodology for these drugs, in general, will be approached in a manner consistent with methods presented for drugs that are absorbed and where that absorption is meaningful.

Thus, we are concerned with measures of the release of drug from a formulation and its availability to the body. BE can be simply defined by the relative bioavailability of two or more formulations of the same drug entity. According to 21 CFR

* Deceased (1929–2011).

320.1 [1], BE is defined as "… the absence of a significant difference in the rate and extent to which the active ingredient or active moiety… becomes available at the site of drug action when administered… in an appropriately designed study."

BE is an important part of a new drug application (NDA) in which formulation changes have been made during and after pivotal clinical trials. BE studies as part of abbreviated NDA submissions, in which a generic product is compared with a marketed, reference product, are critical parts of the submission. BE studies may also be necessary when formulations for approved marketed products are modified.

In general, most BE studies depend on accumulation of pharmacokinetic (PK) data, which provide levels of drug in the bloodstream at specified time points following administration of the drug. These studies are typically performed, using oral dosage forms, on volunteers who are confined to a clinical facility (housed) during the study to ensure compliance with regard to dosing schedule, food consumption, activities, and other protocol requirements. This does not mean that BE studies are limited to oral dosage forms. Any drug formulation that results in measurable blood levels after administration can be treated and analyzed in a manner similar to drugs taken orally. For drugs that act locally and are not appreciably absorbed, either a surrogate endpoint may be utilized in place of blood levels (e.g., a pharmacodynamic response) or a clinical study using a therapeutic outcome may be necessary. Also, in some cases where assay methodology in blood is limited, or for other relevant reasons, measurements of drug in the urine over time may be used to assess equivalence.

To measure rate and extent of absorption for oral products, PK measures are used. In particular, model independent measures used are area under the blood level versus time curve (AUC), which is a measure of the amount of drug absorbed, and the maximum concentration (C_{max}), which is a measure of both the amount of drug absorbed and the rate of absorption. The time at which the maximum concentration occurs (T_{max}) is a more direct measure of absorption rate but suffers from being a quite variable estimate that is highly influenced by the blood sampling regimen.

In this chapter, we will discuss single-dose studies, where blood levels are measured following ingestion of a single dose. Multiple-dose, steady-state studies have been required for certain kinds of drugs and formulations, but recently the US Food and Drug Administration (FDA) has discouraged the use of multiple-dose studies for BE evaluations. One objection to the use of such studies is that they are less sensitive to formulation differences than single-dose studies. On the other hand, multiple-dose studies are closer to reality for drugs taken on a chronic basis. This has been a controversial area.

TWO-TREATMENT, TWO-PERIOD (TTTP) DESIGNS—ANALYSIS OF AVERAGE BE

TTTP, two-sequence crossover designs are commonly used to compare the average BE of two products. The statistical model for this design can be expressed as follows [2]:

$$Y_{ijk} = \mu + G_i + S_{ik} + P_j + T_{t(ij)} + \varepsilon_{ijk}, \tag{11.1}$$

where μ is the overall mean, G_i is the effect of sequence group (i = 1, 2), S_{ik} is the effect of subject k in sequence i (k = 1, 2, 3,…, n_i), $T_{t(ij)}$ is the treatment effect t (t = 1, 2) in sequence i and period j, and ε_{ijk} is the residual error. N, which is the total number of subjects in the study, is equal to $n_1 + n_2$, which, to obtain balance, is generally set as $n_1 = n_2 = n$.

Average BE addresses the comparison of the mean results for each treatment in the BE study and does not consider within-subject variance differences between the treatments or interactions. The design and analysis of the two-period crossover study are relatively straightforward. Subjects are randomly assigned to two dosing sequences. In one sequence, Product A is administered in the first period, and after a suitable washout time, Product B is administered in the second period. In the second sequence, the order of administration (AB) is reversed (BA) as shown in Figure 11.1. The washout is typically at least five to six elimination half-lives for the drug or long enough to have drug concentrations from the first period undetectable just before dosing in the second period. The design typically has an equal number of subjects assigned to each sequence, although this is not necessary for a valid BE evaluation, and unequal subject numbers often occur due to subject discontinuations. Before dosing in each study period and at specified times postdose, blood samples are taken for analysis of drug levels. A typical PK profile of drug levels over time is shown in Figure 11.2. If the drug is one that is present naturally in the blood, then each postdose sample is corrected for the predose (baseline) concentration. This is accomplished by collecting multiple predose blood samples and taking the average of their concentrations as a baseline drug level to subtract from all postdose samples. When the baseline concentration is not constant over time, a predose sample can be collected at the same time of day as each postdose sample to obtain a matched pair. Baseline correction in this case is done by subtracting the concentration of each predose sample from that of its matched postdose sample. The baseline-corrected concentrations provide the primary data for use in the PK evaluations.

The analysis of the drug concentration data consists of determining the parameters C_{max} (the peak value observed), T_{max} (the time at which the peak was observed), and area under the drug concentration versus time curve (AUC) for each subject in each product. AUC is determined using the linear trapezoidal rule, as illustrated in Figure 11.2. The area segments between adjacent concentration-time points (C_i, t_i) are summed from time 0 to time t of the last measured concentration, C_t. This area is designated as AUC(t). The area of a trapezoid is 1/2 Base × Sum of its two sides, where Base = $t_2 - t_1$ and the two sides are the drug concentrations C_1 and C_2 for the adjacent samples at times t_1 and t_2, respectively. The highlighted trapezoid in

	Period 1				Period 2
Sequence 1:	Product A	→	(Wash-out)	→	Product B
Sequence 2:	Product B	→	(Wash-out)	→	Product A

FIGURE 11.1 TTTP design.

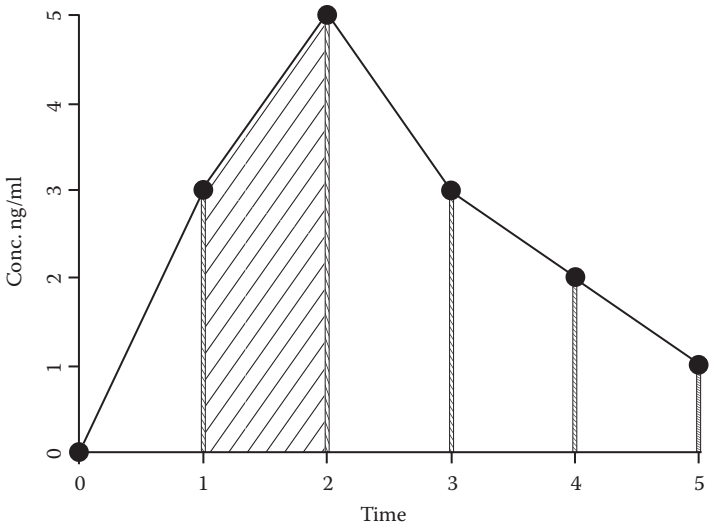

FIGURE 11.2 Typical blood level versus time profile.

Figure 11.2 has area = 1/2 (2 – 1 h) × (3 + 5 ng/mL) = 4 h-ng/mL. C_{max} in Figure 11.2 is 5 ng/mL and T_{max} is 2 h.

In BE studies based on drug levels in blood, three primary parameters are estimated. These are AUC(t), AUC(inf), and C_{max}. AUC(inf) is computed as AUC(t) + C_t/K_e. K_e is the apparent rate of elimination of drug from the blood. The half-life of the drug $T_{1/2} = \ln(2)/K_e = 0.693/K_e$. T_{max}, K_e, and $T_{1/2}$ are considered secondary parameters and for many drugs are not crucial to product approval. If the values of these parameters differ considerably between test and reference products, the FDA may want to know why. T_{max} is sensitive to relatively large differences between products in rate of drug absorption, or in lag-time, time to first measured concentration. The FDA will evaluate T_{max} differences for products where time to onset of drug effect is important to product efficacy. For some products [2,3], the FDA requires evaluation of partial AUCs. These parameters, designated AUC_{0-x} and AUC_{x-t}, split the standard AUC(t) into segments. The FDA has stated that such parameters could be required when the amount of drug absorbed before or after X hours is critical to product efficacy.

Statistical Analysis

The TTTP study design (Figure 11.1) is a variation of a Latin square. In this design, certain effects are confounded and cannot be directly estimated. Confounding means that observed effect [estimate from analysis of variance (ANOVA)] is a combination of two or more effects, and we cannot separate how each effect contributes to the observed value. We attempt to design studies with confounding effects in a way that one effect predominates over the other [2]. Despite not being sure which effect actually predominates, we make an educated guess. For example, a main effect like treatment will usually be more prominent than the interaction treatment × period.

Carryover (CO) occurs when a parameter value in one period is influenced by the treatment received in the previous period. If blood levels in a period differ from what they would have been had the previous period not occurred, we have a CO effect. If the magnitude of this difference does not depend on which treatment was received in the previous period, then the CO effect is designated as a Period effect. Due to the usual practice of having the same number of subjects taking the test and reference product, or nearly so, in each period, the finding of a statistically significant ($P < 0.05$) period effect is not a problem. A Period effect will influence results for all treatments equally, so treatment differences are not affected.

If the magnitude of the CO effect depends on which treatment was previously received, then we have a differential CO effect. In the TTTP study, this is a problem, as it is not possible to adjust the treatment difference for this type of CO.

The sequence effect, in the TTTP study, is the difference between average results for subjects given treatments in the order A followed by B and the average for subjects given treatments in the order B followed by A. Differential CO cannot be measured directly in the TTTP study [2], but its existence can lead to a statistically significant sequence effect. At one time, if a significant sequence effect (at the 0.10 level; $P < 0.10$) was found, the FDA might reject the study results. Unfortunately, this approach rejects 10% of all studies with no true sequence effect, by chance. Despite random assignment of subjects to sequence groups, if subjects in one group truly differ in their PK behavior from those in another group, the sequence effect that arises is unrelated to differential CO. Currently, if blood levels of drug are absent or less than 1/20th of C_{max}, for Period 2 predose samples, the FDA does not consider a sequence effect to be an issue.

Two other effects that are confounded in the TTTP design are sequence × period interaction and treatment effect (i.e., the difference between treatments). A sequence × period interaction occurs when the difference between Periods 1 and 2 results depends on which sequence is evaluated.

Statistical Analysis for BE

Some history may be of interest with regard to the statistical analyses recommended the FDA's most recent Guidance [4]. In the early days of BE analysis, before the late 1980s, a hypothesis test was used at the 5% level of significance. The calculated values of PK parameters, with no transformations, were used in the analysis. The null hypothesis was stated as the products being equal, the alternate hypothesis was that they were not. ANOVA using a statistical model containing terms for Subject, Period, and Treatment Effects was performed. Sequence effects, when tested, were based on dividing the Subject effect into its two components, Sequence and Subject-within-Sequence. *F* tests for all effects had the effect's mean square as the numerator and the ANOVA error mean square error (MSE) as the denominator. In the *F* test for Sequence effects, the MSE in the denominator was replaced with the mean square for Subject-within-Sequence. Any calculated *F* test value exceeding the critical one from the *F* distribution indicated a statistically significant difference for the effect (e.g., Period 1 ≠ 2, Sequence AB ≠ BA, Treatment A ≠ B). There were problems with this approach. Even with large differences between products, if the residual variance (MSE) was large, the large difference might not be detected as significant ($P < 0.05$). The two products could be deemed to be bioequivalent, even when they were not.

The FDA, recognizing this problem, added a requirement that the power to detect a true 20% difference between products had to be 80% or higher. This solves one problem, but another still existed. If power was high (>80%), when there was truly a small difference between products, we could have statistical significance ($P < 0.05$), and we would reject the hypothesis of equivalence. In practice, when a statistically significant difference was small (e.g., ≤10%), a Medical Officer could consider it to be clinically insignificant, and BE was concluded.

Another requirement surfaced at about the same time, the 75/75 rule [7]. This rule required 75% or more of the subjects to have test/reference ratios between 75% and 125%. This appeared to be a logical way to insure "individual" BE. However, the criterion has no statistical basis and often failed drugs with high variability. In fact, if tested against itself, a highly variable product would fail most of the time. The 75/75 rule was correctly phased out.

Sometime in 1987, the equivalence test approach was replaced by one based on the principle that two products could differ by a small amount and still have comparable efficacy. The approach was presented by an FDA biostatistician [8] as the two, one-sided, *t* test (TOST). Shortly after its introduction, TOST began to be implemented using a 90% confidence interval (CI) method. The method required the 90% CI for the difference between test and reference, for both AUC and C_{max} to be entirely within an interval between –20% and +20% of the reference mean (i.e., 0.80–1.20 for T/R).

The following PK expression for AUC suggests a multiplicative model.

$$\text{AUC} = FD/VK_e. \tag{11.2}$$

F is the fraction of drug absorbed, D is the dose, V is the volume of distribution, and K_e is the elimination rate constant. The ln-transformation of Equation 11.2 converts it into the linear relationship, $\ln(\text{AUC}) = \ln(F) + \ln(D) - \ln(V) - \ln(K_e)$, for which statistical analysis is quite manageable. A similar situation exists with C_{max}. For several years, whether to ln-transform the primary PK parameters or not depended on the study data and was decided for each parameter independently by applying a statistical test. This test determined if the parameter appeared to be better described by a lognormal distribution than a normal distribution.

The 90% CI for nontransformed results is calculated as

$$90\%\ \text{CI} = 1 + [((\text{T} - \text{R}) \pm t\,(2S^2/N)^{1/2})/\text{R}], \tag{11.3}$$

where T and R are Test and Reference means, respectively; t is the t distribution value, two-sided, $\alpha = 0.10$, df that for S^2; S^2 is the variance estimate (MSE from ANOVA); and N is the number of subjects with both T and R results.

The 90% CI had to be entirely within 0.80–1.20 for BE to be declared. Equation 11.3 does not give an exact CI in that the true T-R will not be in the 90% CI, 90% of the time. R in the denominator is treated like a constant rather than as the estimate, which it is. This introduces error that is not factored into the CI calculation, which only accounts for error caused by the use of an estimate for the T-R part of the equation. Also, the decision rule is not symmetric. With a product difference equal to

20%, we would have T = 0.80 × R, with T/R = (0.80 × R)/R = 0.80. This same 20% difference when viewed in terms of R/T = 1/0.80 = 1.25. Although the 0.80–1.20 limits provide symmetry for T-R, we need to use 0.80–1.25 for symmetry for T/R.

The 90% CI for ln-transformed results has a simpler form:

$$90\%\ \text{CI} = (\text{T} - \text{R}) \pm t\,(2S^2/N)^{1/2}). \tag{11.4}$$

Analysis Using the Log Transformation

After examining many BE submissions, the FDA concluded that the primary BE parameters should always be log-transformed. This led to a more direct interpretation of study results. The 90% CI on T-R calculated from log-transformed data is mathematically equivalent to the 90% CI on the log of the untransformed T/R ratio. Taking the antilog of this CI, we obtain the 90% CI for geometric mean T/R ratio for our results before transformation. The 0.80–1.25 acceptance range applied to this 90% CI leads to identical BE conclusions whether T-R or R-T is used in Equation 11.4.

For purposes of illustrating the method, ln-transformed C_{max} for the first two periods in 16 subjects who participated in a four-period, fully replicated study (Table 11.1) will be used. ANOVA tables and the 90% CI are shown in Table 11.2. The SAS [6] General Linear Models (GLM) procedure was used to perform the analysis. The SAS program statements are as follows:

```
Proc GLM;
Class SEQ SUBJ PER TRT;
Model LNCMAX = SEQ SUBJ(SEQ) PER TRT/CLPARM ALPHA = 0.10;
ESTIMATE 'T-R' TRT -1 1;
LSMEANS TRT;
```

The data were balanced, $n_1 = n_2 = 8$, so simple ANOVA calculations [2] could have been used. However, if balance does not exist, as often happens when there are subject discontinuations, these simpler calculations do not work and a GLM procedure, which is always applicable, should be used. If the T and R treatments are coded as A and B, respectively, the ESTIMATE statement would have "TRT 1 -1" instead of "TRT -1 1."

The mean square for the subject within sequence term, SUBJ (SEQ), is the correct error term for testing sequence (SEQ) effects, as the sums of squares (SS) and degrees of freedom (DF) for these two terms can each be added to form the SS and DF for SUBJ to simply test for subject effects. Table 11.2 is a summary of the SAS output.

The difference in the mean values for the ln-transformed test and reference values (T-R) is 0.100875, and the residual error (S^2 = MSE) is 0.00953796. The 90% CI calculation (Equation 11.4) is

$$\begin{aligned} 90\%\ \text{CI} &= (\text{T} - \text{R}) \pm t(2S^2/N)^{1/2} \\ &= (0.100875) \pm 1.76[(2)(0.00953796)/(16)]^{1/2} \\ &= (0.100875) \pm 0.0608161 = 0.040059, 0.161691 \end{aligned}$$

TABLE 11.1
lnC_{max} for Periods 1 and 2 from a Four-Period, Fully Replicated Study

Subject	Treatment	Sequence	Period	lnC_{max}
1	Test	1	1	2.639
2	Test	1	1	2.815
3	Test	1	1	2.561
4	Test	2	2	2.632
5	Test	1	1	2.747
6	Test	2	2	2.538
7	Test	2	2	2.599
8	Test	2	2	2.628
9	Test	1	1	2.569
10	Test	2	2	2.865
11	Test	1	1	2.584
12	Test	2	2	2.986
13	Test	1	1	2.347
14	Test	2	2	2.973
15	Test	2	2	3.096
16	Test	1	1	3.096
1	Reference	1	2	2.603
2	Reference	1	2	2.738
3	Reference	1	2	2.472
4	Reference	2	1	2.588
5	Reference	1	2	2.606
6	Reference	2	1	2.650
7	Reference	2	1	2.347
8	Reference	2	1	2.442
9	Reference	1	2	2.603
10	Reference	2	1	2.725
11	Reference	1	2	2.464
12	Reference	2	1	3.144
13	Reference	1	2	2.073
14	Reference	2	1	2.859
15	Reference	2	1	2.741
16	Reference	1	2	3.006

The antilogs of the lower and upper 90% CI limits are 1.04 and 1.18, which are the limits for the untransformed test-to-reference ratio. As the antilog of a mean calculated from ln-transformed data is the geometric mean of that data, the 90% CI just calculated is that for the geometric mean test-to-reference ratio. Had we used R-T instead of T-R, the limits would equal –0.161691 and –0.040059, with antilog values of 0.85 and 0.96, which equal 1/1.18 and 1/1.04, respectively.

TABLE 11.2
ANOVA for lnC_{max} from Table 11.1

Source	DF	Sum of Squares	Mean Square	*F* Value	Pr > *F*
Model	17	1.64431063	0.09672415	10.14	<0.0001
Error	14	0.13353137	0.00953796		
Corrected total	31	1.77784200			
	R-Square 0.924891	CV 3.645142	Root MSE 0.097662		Mean 2.679250
Source	DF	Type III SS	Mean square	*F* value	Pr > *F*
SEQ	1	0.11162813	0.11162813	11.70	0.0041
SUBJ (SEQ)	14	1.45125188	0.10366085	10.87	<0.0001
PER	1	0.00002450	0.00002450	0.00	0.9603
TRT	1	0.08140612	0.08140612	8.53	0.0112
		GLM Procedure Least-Squares Means			
TRT	lnC_{max} LSMEAN				
Reference	2.62881250				
Test	2.72968750				
Parameter	Estimate	SE	90% Confidence Interval		
T vs. R	0.10087500	0.03452889	0.04005891	0.16169109	

The residual error in the ANOVA is assumed to be the within-subject variability, an average of the variability within each treatment. We cannot directly estimate the variability of each product separately, a deficit that has some importance as will be discussed later.

The concept of power in TOST relates to the probability of demonstrating BE. A sufficient number of subjects need to be included to obtain the power desired. If two products are truly bioequivalent (i.e., test/reference is really between 0.80 and 1.25), the greater the subject number in the study, the greater will be the power of demonstrating BE. Although an extremely large *N* leads to high power, in practice, one chooses a sample size that provides good power but is also practical. With TOST (or its 90% CI implementation), the probability of demonstrating BE when products are not BE (i.e., true test/reference ratio <0.80 or >1.25) never exceeds 0.05 regardless of the *N* in the study. Sample sizes for various T/R ratios, within-subject CV, and values of power have been published by Dilletti et al. [9]. A simple Excel spreadsheet providing sample sizes for any desired power, test-to-reference ratio, and within-subject CV is on the CD that accompanies the statistical textbook by the authors of this chapter [2].

The *F* test for sequence effect uses the subject-within-sequence mean square as its denominator. Using the ANOVA results in Table 11.2, the test for sequence

effect (or CO) is $F_{1,14}$ = 0.1037/0.11163 = 0.929, which does not exceed the critical value 4.60.

All primary PK parameters must pass the 90% CI test, 0.80–1.25, for BE to be demonstrated. This includes AUC(t), AUC(inf), and C_{max} for the parent drug and, in some cases, even for metabolites. Most products require single-dose evaluation for BE under both fasted and fed conditions. As noted previously, at the present time, in general, the use of multiple-dose studies is not recommended. There are some products [10,11] that can only be evaluated safely in patients who require the drug on a continual basis, so single-dose studies are not possible and multiple-dose studies must be used. For some NDAs (e.g., controlled-release product with an immediate-release reference product), multiple-dose studies are required. These studies are typically to assess relative bioavailability and are not actual BE ones, as the products being compared do not meet the requirement of being pharmaceutically equivalent, or similar.

REPLICATE STUDY DESIGNS

Replicate studies involve dosing of subjects with at least one of the products being tested dosed on more than one occasion (period). Three- or four-period designs can be used, although, for average BE, the four-period design is typical. The fully replicated (four-period) study reduces the number of subjects required for ABE, as twice the amount of data is obtained for each subject compared with the TTTP study. When healthy, adult subjects are involved, there generally is little reason to use a replicate design. The number of PK samples (drug analyses) is the same, whether a study is a TTTP in N subjects or a fully replicated one in N/2 subjects. When subject recruitment is an issue, the replicated study is a useful alternative to the TTTP study. Recruiting 72 epilepsy patients for a TTTP felbamate study is significantly more costly (time and money) than recruiting 36 for a fully replicated one, even if more patients are added to the four-period study to account for possibly more discontinuations.

The ABE statistical analysis is demonstrated using the results from a two-treatment, four-period replicate design study. Two sequences were used, ABAB and BABA, A = Test and B = Reference. Table 11.1 (Periods 1 and 2) combined with Table 11.3 (Periods 3 and 4) give the ln C_{max} values for the first eight subjects in each sequence group. Because replicated dosing is involved, the GLM procedure for the TTTP study should not be used. The FDA requests that a mixed-effects linear models approach be used. The recommended SAS code [1] is as follows:

```
PROC MIXED;
CLASSES SEQ SUBJ PER TRT;
MODEL LNCMAX = SEQ PER TRT/DDFM = SATTERTH;
RANDOM TRT/TYPE = FA0(2) SUB = SUBJ G;
REPEATED/GRP = TRT SUB = SUBJ;
LSMEANS TRT;
ESTIMATE 'T VS. R' TRT 1 -1/CL ALPHA = 0.1;
```

TABLE 11.3
lnC_{max} for Periods 3 and 4 from a Four-Period, Fully Replicated Study

Subject	Product	Sequence	Period	lnC_{max}
1	Test	1	3	2.854
2	Test	1	3	2.942
3	Test	1	3	2.820
4	Test	2	4	2.556
5	Test	1	3	2.744
6	Test	2	4	2.607
7	Test	2	4	2.621
8	Test	2	4	2.584
9	Test	1	3	2.635
10	Test	2	4	2.718
11	Test	1	3	2.576
12	Test	2	4	3.045
13	Test	1	3	2.503
14	Test	2	4	2.854
15	Test	2	4	2.904
16	Test	1	3	2.947
1	Reference	1	4	2.603
2	Reference	1	4	2.738
3	Reference	1	4	2.472
4	Reference	2	3	2.588
5	Reference	1	4	2.522
6	Reference	2	3	2.438
7	Reference	2	3	2.503
8	Reference	2	3	2.287
9	Reference	1	4	2.573
10	Reference	2	3	2.725
11	Reference	1	4	2.464
12	Reference	2	3	3.066
13	Reference	1	4	2.888
14	Reference	2	3	2.859
15	Reference	2	3	2.859
16	Reference	1	4	2.920

Excerpts from the SAS output are provided in Table 11.4. The 90% CI is 0.0427–0.1460, providing antilog values 1.04 and 1.16. The study, therefore, demonstrates the BE of the test and reference products. The DIAG covariance parameter estimate for TRT Ref (0.02333) is used to estimate intrasubject CV for the Reference product: $CV = 100\% \times (e^{0.02333} - 1)^{1/2} = 15.4\%$. Using that for TRT Test, the test product CV = 8.1%. No comparison of these values is required for ABE.

TABLE 11.4
ABE Analysis of Data from 16 Subjects Completing a Four-Period, Fully Replicated Study

Analysis for ln-Transformed C_{max}

MIXED Procedure

Class-Level Information

Class	Levels	Values
SEQ	2	1 2
SUBJ	16	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
PER	4	1 2 3 4
TRT	2	Ref Test

Covariance Parameter Estimates (REML)

Cov Parm	Subject	Group	Estimate
FA (1,1)	SUBJ		0.1882
FA (2,1)	SUBJ		0.1797
FA (2,2)	SUBJ		8.79E-18
DIAG	SUBJ	TRT Ref	0.02333
DIAG	SUBJ	TRT Test	0.006552

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > *F*
SEQ	1	14	0.38	0.5493
PER	3	34.3	1.12	0.3536
TRT	1	37.6	9.49	0.0039

Estimate Statement Results

Parameter T vs. R							
α = 0.1	Estimate	SE	DF	*t*	Pr > |*t*|	90% CI	
	0.09434	0.03063	37.6	3.08	0.0039	Lower	Upper
						0.04269	0.1460

Least Squares Means

Effect	TRT	LSMEAN	SE	DF	*t*	Pr > |*t*|
TRT	Ref	2.6427	0.05425	14.4	48.71	<0.0001
TRT	Test	2.7370	0.04714	14	58.06	<0.0001

INDIVIDUAL BIOEQUIVALENCE

For at least 25 years, the pharmaceutical industry has struggled with BE evaluations for highly variable drugs (HVD). An HVD is one with intrasubject CV of 30% or higher. High variability can be due to pure biological reasons, such as poor solubility or absorption of the drug in vivo. It can also be caused by poor product formulation.

The drug in the product may have good solubility and absorption, but the poor formulation of the product does not deliver the drug consistently to the region in the gastrointestinal tract where absorption occurs. High variability can be introduced by the mode of product administration. Some products become highly variable when given with, or right after, a meal. Other products may have high variability when administered fasted but not when given with a meal. A number of products have highly variable C_{max} but low-to-modest variability for AUC.

In the following discussions, no distinction will be made between a highly variable drug, a highly variable product, or a product that becomes highly variable when administered under a certain condition. HVD will be used in both the singular sense (drug or product) and the plural one (drugs or products). The statistical methods for HVD apply only to those primary parameters with CV of 30% or higher, whereas those with CV less than 30% should be analyzed by the TOST methods previously presented.

Statistical theory indicates that the variance of the mean from a random sample equals the variance of its N individual values (X_1, X_2, X_3,…, X_N), divided by N. That is, $\sigma^2 = \sigma_x^2/N$. We also know that an individual value or a mean from a sample drawn from a normal distribution, such as for ln-transformed area or C_{max} in a BE study, will reside approximately 99% of the time within a range of -3σ to $+3\sigma$ of its true population value, μ. As σ is proportional to $(1/N)^{1/2}$, the larger the subject number, the greater assurance we have that the sample mean is a good estimate of μ. This is true whether the mean is for μ_T, μ_R, or $\mu_T - \mu_R$, for the ln-transformed primary parameters.

The 90% CI for ABE evaluation on ln-transformed results is formed by adding and subtracting $t(2\sigma_x^2/N)^{1/2}$ from the observed mean T-R. The range of possible values between the lower and upper CI limits expresses the uncertainty that we have about our calculated value. Although we do not know the true value of μ, we do know that, 90% of the time, that value will be within this 90% CI range. In other words, we have 90% confidence that the true value is between the lower and upper CI limits. The t value in the CI calculation also depends on N, decreasing in magnitude, as N increases, toward the asymptotic value of 1.645. For a TTTP study with 6 subjects ($df = 4$), the t value is 2.132; for 36 subjects ($df = 34$), it is 1.691; and for 72 subjects ($df = 70$), it becomes 1.667. This decrease is not dramatic, but it reflects the greater level of trust that our observed mean gets closer to its true value as our sample size increases. This decrease in t helps to narrow the range between the limits of the 90% CI as N increases.

The true value of σ_x^2 is also unknown, so we estimate it as S^2 = MSE from the ANOVA. Neither σ_x^2 nor S^2 directly depends on N, but our confidence that the S^2 is close to σ_x^2 increases with increased sample size. This is not directly reflected, however, in the 90% CI equation.

The width of the 90% CI is directly dependent on $(1/N)^{1/2}$. An obvious way to deal with BE assessments for HVD is to conduct a large TTTP study. This is reasonable if the intrasubject CV is not extremely high. With a true test/reference ratio = 0.95 and CV = 40%, having results from 66 subjects in a TTTP study will provide 80% probability of demonstrating BE. If we have a difficult formulation, so that the true ratio might be as low as 0.93 or as high as its inverse (1.075), the subject number increases to 84 subjects. Studies of this size are difficult, but they can be, and routinely are,

performed. The situation changes considerably for a product like progesterone capsules (Prometrium). C_{max} CV may actually exceed 125%, so with a true test/reference ratio = 0.95 (or 1.053), more than 400 subjects are needed for 80% power. Most in the pharmaceutical industry, and at the FDA, realize that simply going to higher and higher subject numbers is not a satisfactory solution for HVD.

From the early 1990s until about 2002, considerable effort was expended exploring a radically new method for determining BE, individual BE (IBE). The IBE statistic was mathematically derived from a fundamental principle—that the difference for a patient switching between taking reference product and a generic should be comparable with the differences seen from one reference dose to the next. This difference for which the statistic was designed was that for AUC and C_{max}. The derivation of the statistic started with the individual difference ratio (IDR):

$$\text{IDR} = E[\text{T} - \text{R}]/E[\text{R} - \text{R}'], \text{ where } E[X] \text{ is the expected value of } X.$$

As with ABE, the parameters AUC and C_{max} are ln-transformed before evaluation. Accordingly, T – R and R – R′ are mathematically equivalent to ln(*T*/*R*) and ln(*R*/*R*′), where the italicized values represent antilog (nontransformed) values of T, R, and R′.

The IDR is squared to maintain its symmetry, as if there is a critical difference between products, it does not matter if it is because T > R or R > T. By using IDR^2, any 90% CI method is automatically transformed to a one-sided, 95% confidence bound one. The FDA proposed that there should be 95% confidence that IDR^2 did not exceed (ln(1.25))^2. Further derivation led to the IBE expression:

$$[(\mu_T - \mu_R)^2 + \sigma_D^2 + (\sigma_T^2 - \sigma_R^2)]/\sigma_R^2 \le \theta, \tag{11.5}$$

where $\mu_T - \mu_R$ is the difference between the true test and reference means, σ_D^2 is subject × treatment variance (interaction), and σ_T^2 and σ_R^2 are within-subject variances for test and reference treatments, respectively. θ, the regulatory constant, was set to $[\ln(1.25)^2 + \epsilon_I^2]/\sigma_{wo}^2$, with $\epsilon_I = 0.05$ (variance allowance) and $\sigma_{wo} = 0.20$.

With σ_R^2 in the denominator as a scaling device, the IBE criterion becomes less stringent when reference variance is large. Even with a very large T-R difference, two products could be deemed bioequivalent if the σ_R^2 is large enough. This is a natural mathematical consequence of the IDR and should not compromise the basic principle upon which the statistic is based. This can occur even when the observed T-R exceeded ln(1.25). This was viewed by some as a political liability, as the upper limit of 1.25 was ingrained in BE evaluations. To deal with this, the FDA added the restriction that the observed *T*/*R* ratio had to fall between 0.80 and 1.25.

The FDA allowed for a constant scaling factor (0.15) to replace σ_R in the denominator of Equation 11.5 if the estimate of σ_R was less than 0.15 (i.e., $S_{WR} < 0.15$). The fear was that the IBE statistic would become very large, even when T-R was reasonably small, if this S_{WR} happened to be small. Even if S_{WR} became this small, however, the constraint on IDR should occur, although the values for σ_{wo} and ϵ_I, the regulatory constants, might not be appropriate for a product with such low variability.

Despite the years (>6) spent by the FDA to develop the IBE approach, the method was ultimately rejected by both the FDA and, in large part, by the pharmaceutical industry. Its demise seems to have been due to the fact that each of its component terms was understandable. The first concern was that $(\mu_T - \mu_R)$ might become too large. After that, the FDA began to worry about the magnitude of σ_D^2. This surfaced after an internal working group evaluated replicated studies it had in its archives, and a few large estimates of σ_D were found. The FDA's guidance [1] states "A subject-by-formulation interaction could occur when an individual is representative of subjects present in the general population in low numbers, for whom the relative BA of the two products is markedly different than for the majority of the population." The FDA's concern was that a group of subjects might have test-to-reference ratios outside the 0.80–1.25 range, used for ABE. However, it is not known if this standard ABE range is applicable to all drugs. For HVD, it is highly unlikely that 0.80–1.25 is the meaningful range. Even if a product produces results outside this range, the IBE statistic should still provide the constraint desired for the IDR, as the IBE statistic is not solely a function of σ_D. The acceptable magnitude for σ_D became a major issue for the FDA and suggestions were made to place another restriction on IBE, this one to limit the size of the σ_D estimate.

Industry, although happy to have a method for HVD, became increasingly concerned that if IBE was adopted, the FDA would want fully replicated studies for every drug product regardless of variability. This concern increased when in 2001 the FDA requested fully replicated studies for all modified-release and HVD products. The intention was to have a 2-year period in which these replicated studies would continue to be approved by ABE, while the agency performed IBE calculations on real data to evaluate the method. This evaluation period began, and ended, almost simultaneously due to the concerns by both industry and the FDA. By 2002, the outside expert panel that had been formed in 1997 to assist the FDA's internal group to develop the IBE approach received a polite dismissal letter, thanking them for their service to the FDA. No further public meetings were held on IBE, and for some time afterwards, even the mention of IBE seemed to be an anathema to many at the FDA.

SCALED AVERAGE BE (SABE)

With the demise of IBE, how to deal with HVD once again was a debated issue. The IBE statistic had some promising components, particularly the use of a scaling factor. The squared difference between treatment means in the numerator was also nice, as its square root (T-R) was the basis for ABE for many years. The σ_D term was a problem, but ABE evaluations did not parse this from overall variability, and the FDA had never seen a documented case of a true BE failure for hundreds of generic drugs properly approved by ABE. If $\sigma_T^2 - \sigma_R^2$ in the IBE statistic was large, due to $\sigma_T^2 > \sigma_R^2$, then the residual error (MSE) in the ANOVA would increase, making any 90% CI or 95% confidence bound method more difficult to pass. With the troublesome terms removed, the IBE statistic was converted to what we know as the SABE statistic:

$$(\mu_T - \mu_R)^2/\sigma_R^2 \leq \theta. \tag{11.6}$$

An obvious value for θ for SABE was $\ln(1.25)^2/\sigma_{wo}^2$, with σ_{wo}^2 the regulatory constant relevant to evaluating HVD, the stated purpose for this statistical method. The 95% upper confidence bound was adopted for SABE, as had been the case for IBE.

If we take the square root of Equation 11.6, replace θ by its regulatory constants, and do a little rearranging, we obtain an interesting expression:

$$-(\sigma_R/\sigma_{wo}) \times \ln(1.25) \leq (\mu_T - \mu_R) \leq (\sigma_R/\sigma_{wo}) \times \ln(1.25). \tag{11.7}$$

Knowing that $-\ln(1.25) = \ln(1/1.25) = \ln(0.80)$, Equation 11.7 can be rewritten as

$$(\sigma_R/\sigma_{wo}) \times \ln(0.80) \leq (\mu_T - \mu_R) \leq \ln(1.25) \times (\sigma_R/\sigma_{wo}). \tag{11.8}$$

The 95% upper confidence bound, appropriate to the squared statistic, is now transformed to 90% CI, as previously discussed. Equation 11.8 looks very similar to that used for ABE. It is simply the ABE equation with the ln(0.80), ln(1.25) boundaries scaled by the factor σ_R/σ_{wo}. When $\sigma_R > \sigma_{wo}$, a given for HVD, the scaling adjusts the ABE boundaries to something wider.

The concept of widening the BE boundaries for HVD was proposed long before IBE, dating back to the early 1990s or earlier. The European Union's 2010 BE guidance [12] presents a sliding scale for the lower limit [*L*] and upper limit [*U*] for the 90% CI for C_{max} for HVD. The equation for this is given as $[U,L] = \exp[\pm k \cdot S_{WR}]$, where *k* is set to 0.760 and S_{WR} is obtained from the replicated ln-transformed C_{max} results for the reference product. The guidance provides the following example.

Within-Subject CV%[a]	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

[a] $CV\% = 100\% \times (e^{(S_{WR} \times S_{WR})} - 1)^{1/2}$.

Applying Equation 11.8 seems as easy as doing ABE once the BE bounds are determined. The lower and upper BE boundaries depend on the value of σ_R. However, σ_R is not a constant whose value is known, and all that is available is its estimate, S_{WR}. The use of this estimate for σ_R leads to the calculated boundaries being only approximate. They would change from one study to the next, even when the same reference product is used. The error introduced by using S_{WR} is not accounted for in the 90% CI calculation. We are at an impasse with the easy method.

We now return to Equation 11.6 and convert it its equivalent, linearized form [13]:

$$(\mu_T - \mu_R)^2 - \theta\,\sigma_R^2 \le 0. \tag{11.9}$$

In the SABE method, we place a 95% upper confidence bound on the linearized statistic calculated from study-derived estimates for $\mu_T - \mu_R$ and σ_R^2. The SAS program statements for SABE are provided by the FDA in the Guidance for progesterone capsules [14]. If there are equal subject numbers in each sequence, the calculations can be performed in a program like Excel. When there is imbalance in the data, SAS, or a similar package, is a better choice.

The following example of the calculations uses the $\ln C_{max}$ values (Table 11.5) obtained for 30 subjects from a balanced, reference-replicated study. There are 10 subjects in each of the three sequences (TRR, RTR, and RRT). Sequence TRR indicates test product administration in Period 1, reference product in Period 2, and reference product again in Period 3. Sequences RTR and RRT are interpreted similarly. Two quantities are required based on the $\ln C_{max}$ values. The first, designated in the SAS code as "dlat," equals R1-R2, the difference between the first and second reference doses, which will be used to determine the estimate S_{WR}^2, which will replace σ_R^2 in Equation 11.9. The second quantity is the difference between test and reference values, which will be used to calculate an estimate to replace $(\mu_T - \mu_R)^2$. This quantity is designated in the SAS code as "ilat" and equals T-R, where T is the test result and R = 0.5(R1 + R2). Table 11.5 provides the results of these calculations for our example.

The FDA has set θ to $(\ln(1.25))^2/\sigma_{wo}^2$, where $\sigma_{wo} = 0.25$, a value that has had some controversy surrounding it [15,16]. The calculations use R1-R2 and T-R, for each subject, differences between ln-transformed parameter values. As previously discussed, these differences are equivalent to the log of the ratios of the nontransformed values, ln(*R1*/*R2*) and ln(*T*/*R*), where the italicized values are the C_{max} values before transformation. *R* is the antilog of R, so it is actually the geometric mean for the untransformed reference values $(R1 \times R2)^{1/2}$. Note that if one subject had *R1*/*R2* = 9/10 and another subject had *R1*/*R2* = 900/1000, the value for this ratio is identical for both subjects, 0.90. By using a term that is a difference between ln-transformed values in each subject, we remove Subject effects from consideration. This is also true for ilat, the difference T-R. SABE calculations are performed independently by sequence, and then the mean results from the sequences are averaged. This removes Period effects from consideration, the proof of which will not be presented due to its complexity. Once Subject and Period effects are removed, we are left with a simple one-way ANOVA on the dlat and ilat values.

Table 11.6 provides a summary of calculations that will now be discussed. The average of the variance calculated for the R1-R2 values for each sequence is equal to $2S_{WR}^2$, where the 2 arises because two reference values are involved. The three variance values for the $\ln C_{max}$ data are 0.20936, 0.07156, and 0.24845 from the three sequences. The average is 0.17649, which when divided by 2 gives $S_{WR}^2 = 0.08823$. The square root of this value is $S_{WR} = 0.297$, which is ≥0.294, as required for us to use the SABE method. The values for the within-sequence variance for T-R are

TABLE 11.5
SABE Calculations for lnC_{max} Values

TRR Subject	T	R1	R2	R	R1-R2	T-R
2	4.7875	5.0814	4.3307	4.7061	0.7507	0.0814
5	5.1417	5.1475	5.2832	5.2154	–0.1357	–0.0736
7	5.0434	4.8598	5.2470	5.0534	–0.3872	–0.0100
10	4.8203	5.2311	4.7274	4.9793	0.5037	–0.1590
15	4.8598	5.3660	4.9972	5.1816	0.3688	–0.3218
17	5.3471	5.3799	5.5215	5.4507	–0.1416	–0.1036
22	4.7095	4.8675	5.5530	5.2103	–0.6855	–0.5008
25	5.0499	5.0562	4.6540	4.8551	0.4022	0.1948
28	5.1985	5.6664	5.2730	5.4697	0.3934	–0.2712
30	5.2933	5.4596	5.0370	5.2483	0.4226	0.0450
				Mean		–0.11187
				Variance	0.20936	0.04343
RTR Subject	**T**	**R1**	**R2**	**R**	**R1-R2**	**T-R**
1	4.8675	4.1431	4.6728	4.4080	–0.5297	0.4596
4	5.1417	5.5294	5.7746	5.6520	–0.2452	–0.5103
9	4.9053	5.3181	5.2983	5.3082	0.0198	–0.4029
11	5.6836	6.0259	6.1675	6.0967	–0.1416	–0.4131
13	5.3660	5.6204	5.5835	5.6020	0.0369	–0.2360
16	5.7071	5.4072	5.1120	5.2596	0.2952	0.4475
18	5.2983	5.3706	5.6276	5.4991	–0.2570	–0.2008
20	5.7557	5.4467	5.7900	5.6184	–0.3433	0.1374
23	5.7038	5.8319	5.6058	5.7189	0.2261	–0.0150
26	5.0876	4.8903	5.2470	5.0687	–0.3567	0.0190
				Mean		–0.07148
				Variance	0.07156	0.11880
RRT Subject	**T**	**R1**	**R2**	**R**	**R1-R2**	**T-R**
3	5.7170	5.3132	4.7005	5.0069	0.6127	0.7102
6	4.8828	5.2983	6.1485	5.7234	–0.8502	–0.8406
8	5.0938	5.3279	4.7362	5.0321	0.5917	0.0618
12	5.4806	5.7900	5.8021	5.7961	–0.0121	–0.3155
14	6.0591	5.1240	5.9839	5.5540	–0.8599	0.5052
19	5.2523	6.0355	5.8861	5.9608	0.1494	–0.7085
21	5.2983	5.2364	5.3375	5.2870	–0.1011	0.0114
24	5.2311	4.8598	4.9488	4.9043	–0.0890	0.3268
27	5.1417	5.8493	6.1092	5.9793	–0.2599	–0.8376
29	5.2311	5.2832	5.2470	5.2651	0.0362	–0.0340
				Mean		–0.11209
				Variance	0.24845	0.30615

TABLE 11.6
Calculations for the Upper 95% Confidence Bound on the SABE Statistic

	TRR	RTR	RRT	S^2_{WR}
Var(R1-R1)	0.20936	0.07156	0.24845	0.08823
				Mean
T-R	–0.11187	–0.071475	–0.11209	–0.09848
				Se
Var(T-R)	0.04343	0.11880	0.30615	0.07214
	Uncorrected	Corrected	*x*	*y*
Statistic	–0.06059	–0.06580	0.004494	–0.070292
	Lower	Upper		Lower^2
90% CI (T-R)	–0.22135	0.02440		0.04900
	(T-R)^2	$-\theta S^2_{WR}$	Total Error	
Error	0.04450	0.02298	0.05009	

Upper 95% Confidence Bound = –0.01571

0.04343, 0.11880, and 0.30615, whose average (0.15613) provides the variance for T-R for the study. Dividing this by $N = 30$ and taking the square root of that result, gives the standard error for T-R, $Se = 0.07214$. The T-R means for each sequence (–0.11187, –0.07148, and –0.11209) are averaged to get the T-R value for the study (–0.09848). With balanced data, this value is simply the average of all the subject T-R values, without regard to sequence. Its antilog (0.9062) is the geometric mean test-to-reference ratio, which for our data falls within the interval 0.80–1.25, meeting the point estimate criterion for SABE. Next, we determine if we meet the upper 95% confidence bound criterion.

The linearized SABE statistic is obtained by replacing the unknown parameters (μ_T, μ_R, and σ_R) in Equation 11.9 with their estimates:

$$\begin{aligned}\text{SABE statistic} &= (\text{T}-\text{R})^2 - \theta S^2_{\text{WR}} \\ &= (-0.09848)^2 - (0.79669)(0.08823) \\ &= -0.06059.\end{aligned} \tag{11.10}$$

We use the estimate for T-R, squared in Equation 11.10, to replace $(\mu_T - \mu_R)^2$ in Equation 11.9. This is necessary as, unlike for S^2_{WR}, our estimate for σ^2_R, we cannot directly obtaining an estimate for $(\mu_T - \mu_R)^2$. Squaring T-R gives a biased estimate for $(\mu_T - \mu_R)^2$, so the FDA includes a bias correction in the calculations. Se^2 is subtracted from $(\text{T} - \text{R})^2$ in Equation 11.10, to provide a bias-corrected estimate of $(\mu_T - \mu_R)^2$. In the SAS code, the terms *x* and *y* are used, where $x = (\text{T} - \text{R})^2 - Se^2$ and $y = -\theta S^2_{\text{WR}}$. In our example, $x = 0.004494$ and $y = -0.070292$. As in the SAS code, $(x + y)$ gives the bias-corrected linearized SABE statistic (–0.06580) for our example.

In the upper 95% confidence bound calculation, we need to account for the error (uncertainty) that we have in the SABE statistic value. The error associated with (T-R) is accounted for in the calculation of the 90% CI calculation for T-R. This calculation is identical to that presented earlier for the TTTP study, with the exception that we replace $(2S^2/N)^{1/2}$, the standard error for T-R in the TTTP design, with the *Se* value calculated by the SABE method. The degrees of freedom for the critical, two-sided, $\alpha = 0.10$, *t* value (*t*) equals the total number of subjects *N* minus the number of sequences 30 – 3 = 27 for our example.

$$\begin{aligned} 90\%\ \text{CI(LL, UL)} &= (\text{T} - \text{R}) \pm (t)(Se) \\ &= (-0.0985) \pm (1.7033)(0.07214) \\ &= (-0.2214, 0.0244) \end{aligned}$$

Taking the CI limit with largest absolute value (–0.2214) and squaring it, we get 0.04900, a value denoted as bound *x* in the SAS code. Subtracting *x* from bound *x*, we get 0.04450, the error caused by the use of $(\text{T-R})^2$ as an estimate of $(\mu_T - \mu_R)^2$.

To calculate the error due to the use of S^2_{WR} to estimate σ^2_R in the $-\theta\,\sigma^2_R$ term (i.e., the use of *y*), the following quantity, designated as boundy in the SAS code, is calculated. Here, *df* = degrees of freedom and $\chi_{0.95,df}$ is the inverse of the left-tail probability for the chi-square distribution with $\alpha = 0.95$, degrees of freedom equal to that (27) for S^2_{WR}. This is designated as chinv(0.95,dfd) in the SAS code.

$$\begin{aligned} \text{bound } y &= (y)(df)/\chi_{0.95,df} \\ &= (-0.070292)(27)/40.1133 \\ &= -0.0473 \end{aligned}$$

The error associated with the use of *y* is obtained by subtracting *y* from bound *y*. In our example, this error is (–0.0473) – (–0.070292) = 0.02298. The two calculated error values are each squared and summed, and the square root of the result is taken to estimate the total error involved with the SABE linearized statistic. In the example, this total error is $((0.04450)^2 + (0.02298)^2)^{1/2} = 0.05009$.

The calculation of the upper 95% confidence bound is the addition of the bias-corrected linearized statistic $(x + y)$ and the total error $((\text{bound } x - x)^2 + (\text{bound } y - y)^2)^{1/2}$, which for our example is (–0.06580) + (0.05009) = –0.01571. This meets the criterion that the upper 95% confidence bound is ≤0. Having met the point estimate criterion and this statistical criterion, we conclude that our study has demonstrated the BE of the test and reference products.

THE FUTURE

We currently face BE challenges for large molecular drugs, biosimilar products, topical products without meaningful systemic drug absorption, and nonconventional dosage forms. In each of these cases, standard BE measures may not be appropriate or

may be insufficient. Immediate attention seems to be focused on how to properly evaluate BE for Narrow Therapeutic Index (NTI) drugs. Controversy surrounding the use of standard ABE methods for these drugs is not new, but there seems to be intensified interest at the FDA to address the problem [17]. NTI drugs require maintenance of drug concentrations within a narrow window between the minimum effective concentration (MEC) and the maximum tolerated concentration (MTC). For many NTI drugs (e.g., anticlotting agents, heart rhythm regulators, antiepileptic agents, and bronchodilators) when concentrations stray outside the therapeutic window, the consequences for a patient can be life-threatening. Standard ABE limits of 0.80–1.25 may not insure that generic products meet these requirements. Considerations such as narrowing these limits to 0.90–1.11 have emerged as well as possibly placing a point estimate restriction upon the observed test-to-reference ratio. The former suggestion may have some merit, but the latter, point estimate one, has some serious statistical issues. Stricter ABE criteria might constrain the mean generic-to-reference ratio enough that, on average, the generic product drug concentrations reside within the MEC-to-MTC window in a manner comparable with the behavior of the reference product. However, this is unlikely to ensure that this behavior occurs consistently. This latter issue is one related to the within-subject variability of the generic product relative to that of the reference product. We would want $\sigma_T^2 \leq \sigma_R^2$. Consequently, in addition to a 90% CI requirement (95% might be warranted), a separate evaluation comparing σ_T^2 and σ_R^2 may be needed. This might be accomplished by adding another of the discarded IBE terms, $\sigma_T^2 - \sigma_R^2$, into the SABE statistic: $[(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)]/\sigma_R^2 \leq \theta$, with θ set to a value reasonable for an NTI drug. It is not inconceivable that we may find further regression toward the discarded IBE statistic, although hopefully this time the concern will only be with how the composite statistic functions rather than getting alarmed by its individual component values.

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12 Outsourcing Bioavailability and Bioequivalence Studies to Contract Research Organizations

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WHY OUTSOURCE?

What Is the Goal/Reason for Outsourcing?

Contract research organizations (CROs) provide a much needed service to the pharmaceutical sector. Full-service CROs offer a comprehensive selection of capabilities, whereas smaller "niche" CROs may focus on a narrow segment of services (e.g., clinical or analytical only). All of these organizations fulfill a need in that they provide the services necessary for the approval of new clinical entities or generic drug products. A sampling of these services is included in Table 12.1.

Many of the larger pharmaceutical companies have in-house capabilities for most, if not all, of these services. For example, many often have their own clinical and bioanalytical units that provide full support for Phase I studies. However, even these internal resources can become saturated due to the drive to develop more compounds in shorter time intervals.

Unlike their larger counterparts, the smaller companies, virtual firms, and generic companies do not have the luxury of their own dedicated clinical unit or

TABLE 12.1
Check Sheet Providing Typical Services Outsourced for BA/BE Studies

Service	Sponsor (✓)	CRO (✓)
Bioanalytical Analysis		
Bioanalytical Site Selection and Qualification		
Clinical Study Design		
Clinical Protocol Development		
Clinical Site Selection and Qualification		
Clinical Conduct		
Clinical Monitoring		
Data Management		
Pharmacokinetic Analyses		
Statistical Analyses		
Pharmacokinetic Report Writing		
Integrated ICH Report Writing		
Project Management		
FDA/Regulatory Consultation		

full in-house capabilities and are required to outsource their clinical trials, including bioavailability (BA) and bioequivalence (BE) studies. Although generic companies have internal resources for product development, manufacturing, and release testing, they do not have clinical and bioanalytical capabilities.

It is critical that the CRO and client realize the importance of close collaboration and seamless communication between their organizations. This collaboration is necessary to achieve study success in a timely manner. Key elements necessary for success include the following:

- *Communication* at all levels between the CRO and the Pharmaceutical Company
- *Sensitivity* to both the project specific requirements and timelines
- *Flexibility* to recognize and adjust to unexpected events throughout the project timeline

As the number of outsourced services may vary with each client, it is important that the CRO demonstrate a flexible attitude and responsive approach that will enable a better partnership with the Pharmaceutical Company.

Outsourcing Relationship: Vendor versus Partnership

Before selecting a CRO, a company needs to evaluate their goal for outsourcing and assess the relationship they wish to have with the CRO. The most common relationships include the CRO as a vendor, a preferred provider, or a development partner.

Vendor

Some projects may require only a "one-off" type of relationship; that is, the outsourced project is a one-time event and there is no need for a long-term relationship with the CRO. Some questions that need to be resolved include the following:

- Is the project a one-time event?
- What is most critical to the company: timing or cost?
- Will the deliverable be a commodity that is awarded to the CRO with the lowest price?
- Will the study be awarded to the CRO with the earliest dosing date and fastest timelines?
- Does the firm require a single-service CRO (e.g., bioanalytical services)?

Outsourcing managers are cautioned to avoid the "commodity" mindset. Many CRO services are considered to be or are evaluated as if the service was a commodity. Commodities are purchased based on price; quality and value are all considered to be equal (between brands, or CROs). Unfortunately (for the accountants), this mindset is not generally successful in the drug development arena and the phrase "you get what you pay for" is applicable. In the long run, it is important to also focus on quality, timelines, and service level when considering contracting a single service.

Preferred Provider

A preferred provider or vendor relationship/agreement works in two directions. It is assumed that the company or sponsor prefers to give work to those companies with which it has developed this relationship. In return, the CRO is expected to provide better than average timelines and prices. Often, these agreements provide for a tiered discount (i.e., the more studies that a client places with the CRO, the greater the discount on the pricing).

Partner

As mentioned above, an effective CRO-client relationship requires close collaboration and seamless communication to achieve study success in a timely manner. The best outsourcing results are obtained when pharmaceutical firms develop a long-term partner relationship with a quality CRO (or at least assume a partner "mentality" or perspective).

Partners work toward a common goal and benefit. It is important to realize that CROs are made up of individuals who value their work. To them, their work is more than just a commodity. Partnering with these individuals results in a feeling of ownership; this type of relationship will motivate individuals to go beyond the minimum requirements and will result in a higher-quality end product.

As a full development partner, a CRO will help to develop the entire program. As a partner, the CRO has a vested interest in the success of the program and will run with it as if it were its own drug product. Virtual pharmaceutical companies that do not have the in-house expertise for full development must rely on consultants or

a full-service CRO to assist with the successful development and execution of their program. Although most CROs do not provide the capabilities for full partnership, a few have demonstrated that they can successfully develop a drug product from inception to clinical proof-of-concept.

Timing/Cost Considerations

Outsourcing becomes attractive, even to those companies who have in-house resources, when these resources are committed to different projects. Timing and costs are two major considerations that come into play when a pharmaceutical company decides to outsource.

Timing is a major consideration for many projects. Although most Phase I studies are not a critical path to an new drug application (NDA) submission, there are times that BA data are necessary to design a Phase II or III study. Occasionally, a BE study, comparing the Phase III formulation with the final marketed product, becomes rate limiting for an NDA submission. At these times, outsourcing is necessary and cost effective because approval (and marketing) delays can be quite costly when compared to lost revenue.

Generic BE studies are often on very tight timelines because the company's objective is to file an abbreviated NDA (ANDA) within 3 to 4 months of manufacturing the clinical lot. The goal of most generics is to be the first to market because the first generic approval provides that manufacturer with a higher profit margin. Each additional approval increases competition and decreases prices (eroding margins). Timing is even more critical when a generic manufacturer intends to file an ANDA with a Paragraph IV patent certification. The first generic to file (as a paragraph IV) is entitled to 6 months of exclusivity (i.e., no generic competition). Six months of exclusivity (for branded or generic products) provides a substantial financial incentive to the pharmaceutical firm. Therefore, because it is critical that the BE trial be completed expeditiously, these companies approach CROs to provide dedicated resources that can meet the company's timeline.

For those studies where timing is not critical, many companies evaluate cost as a basis for outsourcing. These companies will send a request for proposal (RFP) to a number of CROs. The CROs, in turn, will provide study quotations that detail the price for the services. Interestingly, many companies will compare internal costs versus the cost to outsource. However, this comparison often includes only "out-of-pocket" costs (internal salaries) and does not include overhead expenses (benefits, offices, computers, training, etc.).

It is important to compare "apples to apples" when comparing costs/prices (both internal and external). Companies comparing internal costs should utilize all costs (not just salaries). When comparing bids from multiple CROs, it is also important to assess both the prices and deliverables from each CRO. An RFP that is not clearly written may yield a number of proposals with a wide range of prices. It is important for each CRO to identify the assumptions and deliverables behind each proposal. Firms may be disappointed with the end results if they select a CRO based on price alone.

IDENTIFICATION OF APPROPRIATE CROs

It is important that your CRO has validated corporate procedures for all segments of clinical study conduct. These procedures are used to ensure that all aspects of a study, including but not limited to clinical conduct, laboratory analysis, data management, biostatistics, pharmacokinetics, and medical writing, are performed in compliance with Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and other applicable regulatory practices and guidelines. These procedures, in short, guarantee the credibility of the data and protect the rights and integrity of the study subjects.

Assessment of Capabilities and Experience

Before "shopping" for a CRO or vendor, a company needs to first identify specific services to be outsourced. If the pharmaceutical company has project management resources available, then it may be able to work with multiple vendors to complete a single study. For example, the company could separately contract with a clinical facility (a university clinic, a commercial standalone clinic, or a CRO with clinical capabilities), an analytical unit, and a pharmacokineticist to write the report. Note that the company could also contract the project management duties to one of these three vendors. Alternatively, the company could contract with a CRO that provides clinical, bioanalytical, pharmacokinetic, statistical and report writing services. This "one-stop shopping" generally facilitates the conduct of these studies, assuming that the CRO can provide the experience and meet the company's timeline and pricing expectations.

To identify the CRO that will conduct a potential study, it is necessary to first develop a list of potential CROs. The list will be made up of those CROs that provide all services and those that provide clinic-only or analytical-only services. The list is often composed of those CROs with which the company (or individuals) has worked with in the past. Although there are many CROs that advertise in the trade publications, most of these will not have the necessary BA/BE expertise or capabilities that are required for the study. Thus, the company will need to evaluate all CROs and will need to make the initial "cut." Evaluating the experience and capabilities of the CRO and their ability to meet the company's timeline are the first two screening criteria. For the purpose of this discussion, it is assumed that the pharmaceutical firm will use a single CRO for all services. For those companies who prefer to subcontract the clinical, bioanalytical, and pharmacokinetic resources, the mechanism to identify the most appropriate vendor is the same but must be repeated for each vendor.

Clinical Capabilities

The first step to CRO qualification is the assessment of their capabilities and experience. The ability of a CRO to recruit a particular patient or volunteer population is a primary requirement. The CRO should be able to recruit the entire study population at a single center, preferably as a single group. Healthy volunteer populations are the easiest to recruit; however, some studies may require large numbers of subjects or

replicate designs. In these cases, the ability of the CRO to recruit this large population as a single group should be assessed. When conducting replicate design studies, the dropout rate is often higher than a simple two-period crossover design. As always, the CRO clinic should be capable of recruiting an adequate number of subjects to account for dropouts. Some drug products also require special populations. For example, estrogens are generally dosed to postmenopausal females. Other drugs may be targeted to an elderly population. It is essential that the CRO be assessed for its ability to recruit these special populations.

Bioanalytical Capabilities

Just as the clinical capabilities must be assessed, the bioanalytical capabilities are equally important. Validation lists (lists of analytical methods that are currently available and validated) are available from most CROs. It is critical that the bioanalytical facility be experienced in analyzing the drug (and metabolite, as appropriate) and should be able to provide a written validation report. The validation should be assessed before awarding the study or at least before dosing. In addition to having an appropriately validated method, the facility should follow current GLPs (cGLPs) and have a clean U.S. Food and Drug Administration (FDA) inspection history.

Pharmacokinetic Capabilities

Most companies focus primarily on the clinical and bioanalytical capabilities for CRO selection. However, the pharmacokinetic capabilities should also be critically assessed. The CRO should have validated pharmacokinetic and statistical programs in place and should be compliant with 21 CFR Part 11 (especially in regard to change control).

Timeline Assessment

The list of CROs that meet the company's clinical, bioanalytical, and pharmacokinetic criteria must be assessed for their ability to meet the company's timeline. The CRO must be able to meet the timelines as established by the company management team. In the rare instance that no CRO can meet the timeline, then the company may need to reassess their strategy and internal submission timelines.

Often, the large list of commercial CROs and/or laboratories can be whittled down to between one and three candidates at this point. Once the list has been narrowed, the candidate CRO sites should be evaluated "in person." If, however, too many sites are viable candidates, the sites can be "interviewed" via telephone to evaluate their qualifications. However, the final candidate should be qualified with an on-site inspection.

CRO QUALIFICATION

Due Diligence

If the pharmaceutical firm has used the CRO in the past, they should objectively evaluate their past experience with this CRO. If the experience was good, the firm

should identify those components that were successful and ensure that they are used for their new study. However, caution should be exercised and due diligence pursued if the new study requires a different subject population or analytical technique. For example, a CRO may specialize in recruiting healthy male and female volunteers but may have difficulty in the recruitment of postmenopausal females. Similarly, a successful bioanalytical project using liquid chromatography does not guarantee success with more complex methods such as liquid chromatography–mass spectrometry. On the other hand, if the firm had a negative experience with a particular CRO, the firm should objectively assess the cause of that experience.

All CRO evaluations should begin with an assessment of information in the public domain. The firm should obtain copies of past FDA inspection reports (483's and Establishment Inspection Reports) through the Freedom of Information. Also, the firm should request any FDA warning letters that may have been issued to the CRO.

The CRO should provide the client with a written and signed statement that neither the CRO nor any of its employees or any subcontractors has been debarred by the FDA (under the provisions of the U.S. Generic Drug Enforcement Act of 1992). The CRO should also provide performance metrics used for tracking timelines and financial metrics. The company should request "references"; these references should include those companies that outsourced studies that resulted in successful ANDA or NDA approvals.

The firm should carefully evaluate any external providers (subcontractors) that the CRO proposes to employ (e.g., clinical laboratories, medical specialists, and specialized assay laboratories). The success of the clinical program (in this case, a BA or BE study) is dependent on the weakest link.

Another important aspect (but one that is difficult to objectively assess) is the support that will be provided by the study program manager. This individual is responsible for overseeing of the various functions within the CRO and often functions as the "program champion" and must be capable of managing a multidisciplinary development team. The program manager also manages timelines and serves as communication facilitator within the CRO team and between team and sponsor. This individual has a focus on overall objectives with eye on the final deliverable and timelines.

The larger CROs have expertise in a number of therapeutic areas and can provide consulting capabilities if needed. Although some CROs provide some limited gratis consulting, the real expertise is usually available on an hourly billing rate. The consulting that is available in the larger CROs covers regulatory, medical, clinical, biopharmaceutics, pharmacokinetic, and statistical issues. Availability of this consulting is key when the "unexpected" happens during the study conduct. The unexpected can include analytical failure or unanticipated adverse events, abnormal pharmacokinetic behavior, or inability to prove BE.

After evaluating the credentials and performance metrics of each CRO, the sponsor should physically visit and audit the clinical, bioanalytical, and pharmacokinetic capabilities of the CRO.

Clinical Site Qualification/Audit

The sponsor should conduct a site qualification visit. In addition to a cGCP site audit, this evaluation should include an assessment of the areas in Table 12.2.

TABLE 12.2
List of Those Areas to Be Included in the Clinical Site Assessment

	Check (✓) When Complete
Clinical Site Evaluation	
Assess the volunteer (or patient) population pool	
Evaluate CRO procedures for adverse effects investigation	
Assess training records for the clinical team	
Evaluate CRO's ability to coordinate plasma/urine shipments to different bioanalytical facilities	
Assess ability to coordinate functional handoffs (e.g., timely delivery of protocol to clinic, samples to laboratory, and bioanalytical data to the pharmacokineticist)	
Assess clinical project management capabilities	
Clinical Data Management	
Assess the validation of the data collection system	
Evaluate query generation, SOPs, CRF, and database correction, change control	
Evaluation of Clinical Deliverables	
CRFs (CRO or sponsor format)	
Database (when applicable)	
Blood/plasma/urine collection procedures/SOPs and transport procedures to bioanalytical unit	
Content of the written clinical report (i.e., CRO clinical report to be incorporated into the final study report)	

Bioanalytical Site Qualification

Candidate CROs for bioanalytical laboratory work (for drug, metabolite, and/or biomarker assays) should also be assessed. The personnel and their qualifications and analytical method and validation should be assessed before awarding the study. The company audit should also include cGLP compliance and an assessment of the laboratory's inspection history. Copies of the inspection history with all FDA 483's and Establishment Inspection Reports should be reviewed. Laboratory project management should be assessed for their ability to coordinate all processes with the client, clinic, and pharmacokineticist.

Finally, the CRO should provide written documentation as to the content of the final analytical report that should contain additional project specific validation data (e.g., frozen matrix stability determined for the length of sample storage; i.e., from time of first clinical sample collection to the time that the last sample is analyzed) to support the BA/BE study. The FDA requires that full validation be performed to support BA and BE studies in NDAs and ANDAs [1,2].

Pharmacokinetic Site Qualification

The pharmaceutical firm should also qualify the CRO site (or department) that is responsible for pharmacokinetic and statistical analyses and completion of the final

integrated report. The group should have all programs fully validated according to the FDA programming guidelines. During the pharmacokinetic site audit, the following areas should be carefully assessed:

- Qualifications of pharmacokinetic and statistical personnel.
- Validation of pharmacokinetic and statistical programs (usually SAS).
- Compliance with 21 CFR Part 11. At the time of this publication, full and complete compliance with Part 11 was not being enforced. However, the CRO should have a written plan and timeline for bringing all postlaboratory functions into compliance.
- Evaluation of format and completeness of pharmacokinetic tables and graphs, statistical output (listings), and a mock final report.

Culture

Although culture cannot be quantitatively assessed, it is important to consider the following key areas.

- Is the culture of the CRO compatible with that of the pharmaceutical company?
- Does the firm expect the CRO to make all decisions with regard to minor protocol deviations?
- Does the firm wish to manage all communications and decisions?

COMPETITIVE BIDS/DEFINING THE DELIVERABLES

In an effort to quickly place a clinical study, the development of the RFP may be rushed and result in a document that is subject to various degrees of interpretation. In light of this, it is important for companies to carefully evaluate competitive bids to assure that each CRO has made the same set of assumptions.

Final Report Content and Format

Ideally, the development of an effective RFP and proposal should begin with the outcomes in mind. That is, the focus on the proposal should begin with the objective of a final deliverable (the report) and should include a description of the content and format of the final report.

Final Written Report

CROs work with a large number of different clients; each client often has their own report format preferences. Therefore, if the RFP does not specifically address the report format, the CRO often will make an assumption regarding the report format. This assumption may or may not be explicitly stated in the resulting proposal. This assumption can make or break a proposal because the report format assumes a number of other important deliverables.

A full International Conference on Harmonization (ICH)–formatted report requires a substantial amount of data analysis of all data in the Case Report Forms

(CRFs). Thus, the CRO statisticians will provide additional statistical tables, analysis listings, and graphs. This additional work increases the cost of the study due to the additional statistical and medical writing man-hours needed. Although these data may be required for an NDA BA study, they are not required for a generic BE study.

Many CROs have developed their own "standardized" format for BE studies, which, although quite abbreviated, is adequate for submission to the FDA Office of Generic Drugs (OGD). These reports include a relatively short summary of the clinical and analytical conduct and the pharmacokinetic and statistical results. The clinical report, analytical report, CRFs, and statistical output are merely attached to the report as supportive documentation. This report format requires fewer man-hours and is substantially less expensive that its ICH counterpart. However, the FDA is recommending that even these BE summary reports be prepared in common technical document (CTD) format. It is recommended that sponsors proactively discuss report format requirements with CROs.

If the client requires a report that may also be submitted (at a later date) to the European authorities, then they may expect a CTD (or eCTD) formatted report. However, if the CRO assumes a report formatted for OGD (i.e., not CTD formatted), then the client will not be satisfied with the final product (i.e., report). On the other hand, if the CRO assumes that an ICH format and content are necessary, but the client requires only the more abbreviated OGD report, then the price of the study will be much higher than needed. The CRO will appear to be noncompetitive with other CROs that assumed an OGD format.

Submission of Data and Reports to the FDA

The FDA OGD currently requires ANDA applicants to submit information from all BE studies conducted on the same formulation of the drug product contained in an ANDA [3]. In addition, they recommend that BE summary reports be submitted in CTD format; OGD expects BE data to be submitted using data summary tables consistent with CTD-formatted applications; sample tables are available for download [4].

The following tables are required for a BE review:

- Submission summary (or, alternatively, provide an electronic copy of Form 356H)
- Summary of BA studies, which provides study reference numbers, objectives, designs, treatments, and subjects as well as summary statistics for pharmacokinetic parameters
- Statistical summary of comparative BA data (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}), which provides least squares geometric means, ratio of means, and 90% confidence intervals
- Summary of bioanalytical method validation data
- Summary of in vitro dissolution studies
- Summary of formulation data (qualitative and quantitative composition)
- Demographic profile of subjects for each BE study
- Summary of adverse events for each study
- Bioanalytical reanalysis of study samples
- Study information for each study
- Product information with batch numbers and size, potency, and content uniformity

- Summary of subject dropout information for each study
- Summary of protocol deviations
- Summary of bioanalytical standard curve and quality-control (QC) data
- Standard operating procedures (SOPs) dealing with bioanalytical repeats of study samples (the FDA also requires copies of each SOP to be included in the ANDA submission)
- Composition of meal used in fed BE studies

Unless a sponsor intends to create each of these tables internally, the CRO needs to be aware that these tables are required. Special considerations should be given to chemistry, manufacturing, and control (CMC)–related tables that contain data that are not normally provided to CROs. The sponsor must decide (early in the process) as to whether the CRO or the sponsor will provide these tables. If the CRO provides this service, then these data must be provided by the sponsor to the CRO in a timely manner. However, many sponsors consider these CMC data to be highly confidential and may insist that their own regulatory affairs department enter these data.

Clinical

Protocol Development

Before 1999, the FDA OGD published a large number of drug-specific guidances that provided the basic information needed to conduct a generic BE trial. With the publication of general BA/BE Guidance, the Agency "withdrew" the drug-specific guidances. However, in the past several years, the FDA has published approximately 900 BE recommendations for specific products [5]. Most of these guidances provide some protocol design considerations, but sponsors generally are left to their own resources to determine specific guidance on numbers of subjects, timing of blood samples, etc. It is important that an RFP specify the expectations for protocol development. Three possible options exist, each with a different cost structure:

- Level 1: Client provides final clinical protocol.
- Level 2: Client provides protocol "outline," including design and all specifications; CRO provides final protocol.
- Level 3: Client provides objective; CRO provides design and protocol.

Unless the sponsor provides the final clinical protocol (as in Level 1), the following items must be addressed in the RFP to obtain an accurately priced study.

Protocol Format

Some pharmaceutical firms are quite strict when it comes to formatting requirements. If the firm requires the CRO to follow a specific format (developed by the company), then this information (and the format) should be provided within the RFP. On the other hand, many companies do not have a preference for protocol format. They are only concerned that all of the relevant parameters are included in the protocol. For these companies, CROs can often provide a standardized (and shorter) format for less money. Another advantage to using this standardized approach is that

the CRO clinical personnel are often more familiar with the CRO format that will result in fewer questions back to the client.

Clinical Study Population

Many, if not most, BA/BE studies are conducted in healthy volunteers. In the past, apparently to reduce variability and liability, most sponsors chose to perform most BA/BE studies in healthy, young, male volunteers. However, the most recent FDA guidance for BA/BE studies [6] states as follows:

> Unless otherwise indicated by a specific guidance, subjects recruited for in vivo BE studies be 18 years of age or older and capable of giving informed consent. This guidance recommends that in vivo BE studies be conducted in individuals representative of the general population, taking into account age, sex, and race. We recommend that if the drug product is intended for use in both sexes, the sponsor attempt to include similar proportions of males and females in the study. If the drug product is to be used predominantly in the elderly, we also recommend that the sponsor attempt to include as many subjects of 60 years of age or older as possible.

The FDA guidance provides leeway for the clinical study population. However, the RFP needs to specifically address the expected composition of the volunteer population. To expedite recruitment, it is best to use males and females without specifying a specific ratio of males to females. The study population is also defined by the drug product; for example, an oral contraceptive BE study would be conducted only in females, while that for a hormone replacement product should be conducted in postmenopausal females. Given the difficulties in recruiting some of these special populations, it is important that the sponsor define (upfront) the maximum number of dosing groups that may be allowed.

Inclusion/Exclusion Criteria

The protocol inclusion/exclusion criteria such as acceptable ranges for age and weight, race restrictions, and whether smokers will be allowed to participate can affect the clinic's ability to recruit and can have a significant effect on the cost of the clinical trial. The FDA BA/BE guidance [6] continues as follows:

> If the drug product is to be used predominantly in the elderly, we also recommend that the sponsor attempt to include as many subjects of 60 years of age or older as possible. We recommend that the total number of subjects in the study provide adequate power for BE demonstration, but it is not expected that there will be sufficient power to draw conclusions for each subgroup. Statistical analysis of subgroups is not recommended. We recommend that restrictions on admission into the study generally be based solely on safety considerations. In some instances, it may be useful to admit patients into BE studies for whom a drug product is intended. In this situation, we recommend that sponsors and/or applicants attempt to enter patients whose disease process is stable for the duration of the BE study. In accordance with § 320.31, for some products that will be submitted in ANDAs, an IND may be required for BE studies to ensure patient safety.

Because a BA/BE study for any given drug product may or may not require special inclusion criteria, it is best that any expectations be documented in the RFP. These criteria will affect recruitment and the study cost; when comparing proposals

between different CROs, it is best to evaluate any additional assumptions that the CRO made with regard to these criteria.

Laboratory Chemistries/Special Tests/Physicals

The number of laboratory chemistries, physical examinations (by a physician), and special tests (such as electrocardiograms [ECGs], x-rays, blood glucose monitoring, and special biomarkers) will have a significant effect on the cost of the study. Although the protocol may be very specific regarding the timing and numbers of tests, this information must be present in the RFP to provide an accurate proposal.

Dose and Safety Considerations

For most drug products, the reference listed drug (RLD) and strength(s) to be used in the BE study are provided in the FDA "Orange Book" [7]. Generally, the dose of the RLD is safe to administer to healthy volunteers. However, for some drug products, that dose may cause adverse events and the clinical trial will require additional safety considerations. For example, prazosin has a significant first dose effect that is exhibited by marked postural hypotension; prazosin studies usually require that volunteers stay in a reclined position for several hours after dosing and that blood pressure be routinely monitored. Diltiazem and other calcium channel blockers can cause significant AV block; studies with this type of drug should include serial lead II ECGs to monitor for cardiac adverse events.

Because it is in the best interest (and required by the institutional review board [IRB]) for both the CRO and the pharmaceutical company to ensure subject safety, any known adverse events should be communicated early in the RFP process so that safety procedures can be included in the study budget. If this information is left out of the RFP, then competitive bids may or may not include safety considerations (depending on each CRO's experience with the drug) that could result in two proposals with very different prices.

Clinical Conduct

Clinical bids are based on the version of the study outline or protocol submitted with the RFP. A number of factors affect the price of clinical studies. Some of these are shown as follows:

- Population (volunteers vs. patients, males vs. males and females, postmenopausal females)
- Number of volunteers or patients
- Inclusion/exclusion criteria
- Volunteer stipend
- Number of laboratory chemistries and special tests (ECGs, blood glucose monitoring, etc.)
- Dose (with regard to safety and adverse events)
- Washout period
- Number of blood draws and urine collections and times of sampling

Protocol revisions or amendments that change or add services, including but not limited to laboratories, samples, procedures, personnel or clinical summary report writing, will usually require a revised or amended cost quotation.

Clinical Database

A clinical database (which contains all of the information on the CRFs) is not necessary for BE submissions to the OGD. Also, it is rare that such a database would be required by the FDA for a single dose BE or BA study (in volunteers) to support an NDA submission. However, some companies require all CRF data to be entered into a database so that these data can be included in the overall safety database for the NDA. It should be apparent that inclusion of such a database will increase the cost of the study. Companies should carefully review proposals from CROs to determine if such a database has been included.

Bioanalytical

Any bioanalytical method used for a human BA/BE study should conform to current FDA guidance [2] on analytical validation and should be conducted according to the FDA cGLPs.

Bioanalytical Method/Technology Requirements

Ideally, a CRO should have a validated analytical method in place before dosing the clinical trial. On occasion, a pharmaceutical company may need to contract the method development and validation to a CRO. Because the method ruggedness is dependent on the development and validation processes, these processes should be closely evaluated before committing a BA or BE study to any CRO.

Project Timelines and Turnaround Time

Project timelines are highly method specific. Sample analysis timing and throughput should be discussed, understood, and agreed upon before project agreement. Most CROs have standard turnaround times that will apply unless they are otherwise negotiated. It is also important to negotiate the timeline for the final written analytical report; otherwise, standard CRO timelines will be assumed. These standard timelines may be acceptable; however, it is important to get all timelines committed in writing.

Analytical Report and Data Format

If a client-specific bioanalytical report format, template, or file is to be used to record data, the format, template, or file, along with any instructions, must be provided to the laboratory before or with the shipment of samples. Sponsors should be aware that implementation of client-specific formats may result in additional charges.

Assay of Samples from Placebo-Treated Subjects

Generally, samples from placebo-treated subjects are not an issue with BE studies. However, some BA studies may include placebo treatments so that safety can be more appropriately evaluated. For these studies, it is essential to communicate with the CRO regarding the handling and analysis of these samples. All CROs will charge for each sample that is assayed; some CROs will assay all samples, whether or not they were generated in a placebo treated subject. If the firm does not require placebo-treated samples to be analyzed (because they generally will not provide any meaningful pharmacokinetic data), it is important to provide the randomization schedule to the laboratory before analysis.

SOPs

There must be prior agreement and upfront expectations with regard to SOPs. Some firms require that the CRO follow the firm's SOPs, whereas other companies permit the CRO to operate under their own SOPs. Because the scope of work is affected by the SOPs, this specification must be defined during the RFP process and in the CROs proposal.

Bioanalytical Sample Handling, Shipping, and Storage

Samples originating in HIV-exposed or other infectious subject populations may involve liabilities to clients, clinics, couriers, and laboratories. These samples will require special documentation, shipping, and handling. The clinic, shipping service, regulatory agencies, customs authorities, and the bioanalytical laboratory must be formally notified of all special handling requirements before shipment to the laboratory. Thorough documentation of potentially infectious samples must be included with each shipment container.

Incomplete, illegible, or conflicting information in the sample inventory documentation may delay analytical timelines. Most CROs will accept electronic sample inventory information files; these should be received with the samples provided to the CRO with the electronic information that will be used to support the final analytical report.

Sample storage conditions must be described in the protocol and are dependent on the conditions used for the analytical validation. The samples should be stored using conditions consistent with the validation. Long-term storage charges should be negotiated with each CRO.

Quality Assurance (QA)

All bioanalytical data should be reviewed by and released from the laboratory's QA Unit. Although the laboratory may provide data that are reviewed via a QC process, these data should not be considered final until after the QA audit and release. Note that QA approved data are especially important for GLP studies. The timelines for the final QA-approved data and bioanalytical report should be part of the negotiations with each CRO.

Miscellaneous Bioanalytical Billing Practices

As mentioned earlier, most CROs charge on a per-sample pricing basis (based on the number of samples assayed). However, it is important to point out that the sample count may change without the laboratory's knowledge. For example, the study protocol may be altered to dose fewer (or more) subjects or subjects may drop out of the study due to adverse events. Thus, the final analytical price (based on the number of samples received and assayed) may differ from that in the proposal. Also, some CROs charge for additional sample analyses when sample concentrations exceed the calibration range; in these cases, the samples must be diluted and reassayed. Additionally, some CROs may charge for client-requested repeat analyses (e.g., for reanalyzing samples that appear to be pharmacokinetic outliers or fall outside of the calibration range). Although the FDA discourages this practice, many pharmaceutical clients still require aberrant samples to be repeated. In these cases, it is important that the company consider the CRO policy for reassays before awarding a study to any particular CRO.

Pharmacokinetic and Statistical Analyses

Pharmacokinetic Analyses and Statistical Assessment of Pharmacokinetic Data

The costs of providing pharmacokinetic services are dependent on a number of variables. Table 12.3 provides the requirements that should either be available in the protocol or be explicitly stated in the RFP.

TABLE 12.3
Checklist of Pharmacokinetic Study Requirements That Should Be Included in the RFP

	Check (✓)
Pharmacokinetic Analyses	
Noncompartmental	
Compartmental modeling	
Specific Software Requirements	
SAS	
WinNonlin	
Other (specify)	
BE Analysis	
Average BE	
Population BE	
Individual BE	
Number of Analytes and Matrices (e.g., parent drug only in plasma vs. parent plus three metabolites in plasma and urine)	
Enter # plasma analytes	
Enter # urine analytes	
Enter # analytes in "Other" matrix and identify	
Pharmacokineticist Responsible to Evaluate Bioanalytical Data for Aberrant Values	
CRO	
Client	
Analytical and Database File Formats	
CRO	
Client	
Timelines (i.e., expedited turnaround within 1 to 2 days may be a significant cost variable for the CRO)	
Normal	
Expedited	
Other (define)	
Format Requirement of Pharmacokinetic Tables and Graphs	
CRO	
Client	

Statistical Assessments

The costs of providing statistical services are also dependent on a number of variables. This information must be explicitly stated in the RFP or must be available to be extracted from the protocol:

- Because the statistical analysis plan is a long and comprehensive document, the number of review cycles that the client company expects can have significant effect on the cost of this document.
- Expedited timelines for production of statistical tables, listings, and graphs can affect the cost of this deliverable.
- Requirements for client-specific table, listing, and graph formats can affect the cost of these services. Most CROs offer standard formats (which are ready for ICH-recommended NDA appendices). These standard formats should be considered if cost is a significant factor for the client company.
- The number of unique tables, listings, and graphs will affect the cost.
- The complexity of the statistical analyses will affect cost.

PROPOSAL REVIEW

Once the RFP has been compiled and submitted, each CRO will provide a detailed proposal. These proposals should be carefully evaluated to assure that each CRO used the same set of assumptions. This is especially important when the company has submitted an RFP with only minimal information or with information that could be subject to interpretation. When comparing the resulting proposals, it is important to make sure that all of the pharmaceutical company's criteria are met.

Often, study costs contained in proposals from different CROs may be substantially different. These differences may be explained by additional assumptions contained within the proposal. For example, one CRO may have assumed a larger dropout rate (due to adverse events) based on previous experience with the drug. To meet the expected timeline, the CRO may require (a) a larger stipend and (b) to dose a larger number of volunteers to complete the required number of subjects. A different CRO may not have had experience with the drug product and would have based their proposal on dosing and completing the same number of subjects in the RFP while providing a stipend that would be appropriate for drug studies that have little or no adverse events. Thus, it is obvious that a simple comparison of cost alone is not sufficient when evaluating the proposals.

A number of case examples are provided below, which demonstrate some of the proposal differences in BA and BE studies. These cases were selected because they illustrate the dependency of cost on the complexity of the data management, pharmacokinetics, statistics, and final report.

Generic BE Studies

A Generic Manufacturer wishes to outsource a BE study (or studies) intended to establish the BE of their generic formulation with that of the reference listed product.

The goal of this program, then, is to provide a final written report containing all BE data required by OGD, in a format acceptable to OGD. In this case, the CRO should bid on either one or two studies (a fasting and perhaps a fed study [8], depending on the FDA requirement for the food effect study for this particular drug product). Because OGD does not require a comprehensive clinical database, it is not necessary for the CRO to include a database in the proposal. Also, because the client is only submitting the application to the OGD, a fully integrated/ICH formatted report is not necessary. Thus, the proposal should reflect costs for one or two BE clinical studies, bioanalytical services (including report), and a final pharmacokinetic report (with minimal statistics), which provides confidence intervals for C_{max} and AUC.

Generic Scale-Up and Postapproval BE Studies

A Generic Manufacturer wishes to outsource the BE study intended to support the BE of a reformulated solid oral dosage form that is the subject of an approved ANDA. Because the FDA does not require a comprehensive safety database, the CRO should base their costs on a relatively simple BE trial and pharmacokinetic report that establishes the BE of the reformulated drug product (with the reference listed product).

BA or BE Study for a New Chemical Entity (NCE)

A pharmaceutical company is developing an NCE for marketing approval in the United States and Europe. This company is outsourcing a BA study comparing the BA of a tablet (to be used in Phase II and III clinical trials) with that of a solution. This client has determined that they need an ICH-compliant report and a clinical database that can be integrated into their overall NDA safety database. In this case, the CRO's proposal should encompass much more than that in Cases 1 and 2. In addition to clinical and bioanalytical services, the proposal should also include data management, biostatistics, pharmacokinetics, and medical writing.

Drug Interaction Study (BA); Short Turnaround Time from RFP to Proposal

An international pharmaceutical company is developing an NCE for marketing approval in the United States and Europe. This company is outsourcing a drug interaction study; the RFP is based on a draft protocol and the proposal had to be received within 3 days. This client specified that they needed an ICH-compliant report and a clinical database for integration into the NDA safety database.

In this case, one CRO based their costs on the information contained in the summary sections (a single analyte in plasma and a simple statistical analysis), whereas another CRO based their costs on a more in-depth analysis of the protocol. Unfortunately, because the protocol was a draft, it provided contradictory specifications. The second CRO provided a budget based on additional data that required pharmacokinetic and statistical analyses on the parent drug and three metabolites in plasma and urine. Additionally, this CRO included a more comprehensive statistical analysis; obviously, their proposal was significantly more expensive than that of

the first CRO. If the company bases their CRO choice on price alone, then the project would be awarded to the first CRO. Also, if the company did require the more complex analyses, then this CRO will ask for an out-of-scope increase in budget (and could be accused of a "bait and switch"). It is clear that these parties (the client company and both CROs) failed to communicate their assumptions. However, this is a common event when proposals need to be delivered within a short timeframe.

As can be seen with these case examples, it is critical that the CRO and company fully understand the objectives of the clinical trial and the specifications of the deliverables. If the expectations are not clear, then it is incumbent on both parties to communicate, understand, and discuss/confirm all requirements.

CONTRACTUAL OBLIGATIONS BETWEEN CRO AND SPONSORS

Contract terms and conditions provide the best controls that both the company and CRO have with each other. However, in the rush to get a study initiated, contract considerations are often overlooked. These controls are necessary because the FDA holds the company (not the CRO) responsible for any contractor failures. A good contract provides the company with control and remedies in the event of poor contractor performance.

When drafting a contract, the following areas need to be considered:

- Do the individuals responsible for drafting the contract understand the objectives and details of the clinical trial?
- Is the contract specific as to the duties?
- Is the scope adequately defined?
- Is there a legal review by both the company and CRO?
- Are there acceptable objective performance standards? What standards are used to assess performance?
- Is a schedule for critical tasks included? A detailed description of tasks should include monitoring, audits, data handling, and timing of the clinical, bioanalytical, and final report.
- Any contract modifications should include protocol amendments.
- The contract should provide details of mutual responsibilities.
- The contract should provide remedy for contract breech or substandard performance. These remedies include discussion/mediation, arbitration, and refund/rework if performance does not meet contract specifications.
- Does the contract provide for disclosure of the FDA inspections and/or inquiries?
- The contract should address intellectual property (e.g., patents, copyrights, and trade secrets) and use and disclosure of company technology, data, and publicity.

Master Service Agreements (MSAs) are becoming popular with many pharmaceutical firms. These agreements enable companies to work under a single agreement; individual projects are appended as attachments (sometimes called work orders) to the MSA. It is important that each amendment contain precise specifications,

timelines, and any terms that may be different from the MSA. The MSA is a useful concept when it is necessary to quickly begin a study. Because most of the legal wording has already been approved, it is usually easier to append the work order and initiate the project.

PROJECT MANAGEMENT AND TIMELINES

It is important that the CRO appoint a project manager who will be assigned for the duration of the project and will serve as the central contact person. The project manager's responsibilities will include managing the technical and administrative aspects of the study as defined by the company. The project manager will also coordinate the organization, implementation, and management of the study. In addition, the Project Manager will interact directly with the Clinical Project Director, Medical Director, Project CRA and Compliance, Data Management, Biostatistics, Pharmacokinetics, and Medical Writing personnel to ensure the effective and timely completion of the study.

CRO/Client Project Team

Although the goal of outsourcing is to minimize the amount of effort that a company is required to perform, it is still incumbent on the firm to invest resources into study management and to develop the optimal relationship that will drive the program to success.

Project Team for NDA BA/BE Studies

Those companies that outsource NDA BA or BE studies need to assemble a project team that includes individuals from both the client company and the CRO. In addition to the Project Manager, and to facilitate communication of all deliverables and expectations to the CRO, the client company should include representatives from Contracts, Pharmacokinetics (and Clinical Pharmacology if these are different departments), and Biostatistics. As mentioned earlier, although they are not part of the project team, both the CRO and company should identify individuals responsible for finance and legal issues.

Project Team for ANDA BE Studies

ANDA BE studies are often outsourced using very little client company participation. Most services are generally assigned to the CRO. The CRO project team should include the clinical and bioanalytical project managers, a pharmacokineticist, and a statistician.

CRO/Client Team Meetings and Communications

For programs involving multiple studies, a "kickoff" or initiation meeting between the combined project team should be held. This should be a "face-to-face" meeting at a client or CRO facility. To encourage open and frequent communication, regular

team meetings should be held via teleconference. The frequency of these meetings should be specified in the project or program proposal.

RUNNING THE STUDY—THE DELIVERABLES

Prestudy Activities

Regulatory Documentation

Before drug shipment, the sponsor should collect, review, and approve all regulatory documents required under the U.S. Code of Federal Regulations from the clinical site. Some of the more critical documents include the following:

- Protocol signed by the Principle Investigator and approved by the IRB
- IRB approval letter together with a list of IRB members
- Copy of the IRB-approved informed consent form to be used in the study
- Signed FDA Form 1572 and curriculum vitae for the principal investigators and subinvestigators
- Laboratory certification and normal values

Regulatory packets containing this information should be assembled and delivered to the pharmaceutical firm before shipment of drug supplies. Timely collection of these documents is critical to ensure timely shipment of the study drug to the study site. For most studies, it is expected that the client will submit the regulatory packet to the FDA as part of an investigational new drug or ANDA.

Management of the Test and Reference Formulations

It is important for the pharmaceutical company to understand that the reference and test products must be at the clinical site with sufficient lead-time to inventory and repackage according to the randomization. Usually, the sponsor provides all drug products that are to be used in the BA or BE trial. However, some sponsors request the CRO to purchase (through a local retail pharmacy) the reference product for BE studies. It is critical that the sponsor ensures that the CRO will purchase a sufficient amount (determined by the sponsor) of a single lot number and with an expiration date that will cover the duration of the study. Note that, for ANDA BE studies, the sponsor must test the reference product for potency and dissolution.

If the CRO is responsible for repackaging the study drug products (into unit doses for each volunteer) before dosing, then the materials must be compatible with the drug products. This is especially important with labile drug products that may be repackaged days or weeks before dosing. Some clinical units dispense each subject's dose into small paper envelopes. This type of packaging may have an impact on the performance of a labile or hygroscopic dosage form. It is best for the sponsor to provide containers (bottles) that the CRO can use for repackaging the drug products.

Prestudy Monitoring

Many smaller firms often disregard the need for clinical monitoring. However, some monitoring is needed to ensure that all regulatory procedures are being met and

that the study is conducted according to the protocol. The following areas should be reviewed with site personnel during the initiation visit:

- Background information, including the Investigator Brochure for the study drug and/or the product package insert(s)
- Protocol, study procedures, and associated forms
- Regulatory requirements
- Personnel training records
- Ensure appropriate signed informed consent exists for each study participant
- Review investigator study files for completeness

Project Initiation Meeting

Before the study conduct, the CRO should hold a kickoff meeting that includes all departments (e.g., clinical, analytical, pharmacokinetic, data management, biostatistics, and medical writing) and the client. If more than one CRO is involved, then representatives from each CRO should be in attendance. The following areas should be reviewed:

- Provide contact information for all project team members (including the client project team members)
- Background information, including the Investigator Brochure for the study drug and/or the product package insert(s)
- All study procedures within the protocol
- CRFs
- Monitoring visit schedule
- Regulatory requirements
- Statistical analysis plan
- Handoffs to other departments/CROs
- Shipment of specimens for bioanalysis
- Data transfers (including CRFs, database, bioanalytical data, and statistical and pharmacokinetic data)
- Timelines

Conduct of the Clinical Trial

Assuming that the protocol was clearly written, most outstanding clinical questions should have been addressed during the kickoff meeting and the clinical portion of the study should run with minimal sponsor input. However, the sponsor should not become completely complacent. It is advisable to visit the clinic at least once to monitor the first dose of the study. Ideally, this visit should begin the day before dosing to review regulatory compliance and to physically observe dosing and execution of the protocol procedures (which often begin by 7:00 a.m.).

Clinical Monitoring

If the sponsor does not have in-house clinical monitoring capabilities, this task can be assigned to the CRO. If this is the case, the monitor should be independent of the clinic to prevent any possible conflict of interest.

Concurrent Monitoring

Concurrent monitoring (especially monitoring the first dose) allows the sponsor to assure that the protocol is being conducted according to the written specifications. The tasks that need to be completed at this time include the following:

- Ensure appropriate signed informed consent exists for all study participants
- Review investigator study files for completeness
- Ensure investigator compliance to the study protocol
- Tracking protocol violations and/or protocol deviations
- Review source documents for serious adverse events
- Review drug records
- Provide written site monitoring reports

The clinical monitor should provide written site monitoring reports. Because of the relatively short study duration, most BA/BE studies require minimal monitoring. For example, the monitor could observe the dosing procedures in the first study period and return for a closeout visit after study completion. Additional monitoring during the study can be accomplished via telephone. Items that should be covered in these calls include verification of patient/volunteer enrolment status, review study progress, answer protocol questions, discuss CRF completion, and ensure the study proceeds in a timely manner. The sponsor should document (in writing) these site contacts, including any relevant observations, discussions, questions, and commitments.

Study Close-Out Monitoring

A final closeout visit should be conducted after all subjects have completed. This visit should include the following:

- Compare 100% of the CRFs to the source documents
- Review the CRFs and source documents for serious adverse events
- Resolve CRF queries
- Review drug accountability
- Review investigator study files for completeness
- Ensure investigator compliance to the study protocol
- Review of record retention per the FDA requirements
- Review drug product accountability and reconcile number of dosage units for the FDA compliance

Clinical Review of CRFs and Query Resolution

The Clinical Project Manager and Investigator should review all CRFs. These individuals should evaluate the following elements:

- Accurate transcription of data from source documents to the CRF
- Accurate and appropriate documentation of adverse events
- Overall study conduct and protocol compliance

- Identification and documentation of potential protocol deviations or violations
- Appropriate use of medical terminology
- Correlation of all clinical information

Data Management

Data Management for ANDA-Track Studies

The OGD does not require an electronic database containing all CRF data for BE trials. However, they do require that the "paper" CRFs be submitted with the final report. The complex data management tasks (necessary for many NDA-track programs) are not necessary for ANDA studies. However, the clinical CRO must report data in sufficient detail to provide a clinical report that includes demographics, adverse events, and blood sampling time deviations. These data will be used in the pharmacokinetic/statistical calculations and in the completion of the final study report. In addition, the clinical CRO must provide BE clinical summary tables in CTD format (described earlier).

Data Management for NDA-Track Studies

With the advent of electronic data capture, many clinical CROs do not require the data management function needed for NDA trials that utilize paper CRFs. However, some sponsors still require completion of paper CRFs that are specifically formatted for that organization. These organizations will require a significant data management component for the study conduct. For these studies, a Clinical Data Management Project Manager compiles a data management plan that describes the processes and specifications to be used in the project. This plan includes documentation, logic, and processes for data review and validation, critical timelines and milestones, and timing and types of management reports. The client company should carefully review this plan to assure that the database will integrate with the overall NDA safety database.

Statistical Analysis of Safety Data

As mentioned earlier for Data Management, the OGD does not require a statistical analysis of safety data for ANDA BE studies. However, many sponsors still require that NDA BA studies include these analyses. The statistical analysis of the study "safety data" is usually conducted in parallel (at the same time) with the blood/plasma bioanalysis.

When statistical analyses of safety data are required, the CRO should develop detailed specifications for the statistical analyses and tables production. Generally, the programming is done within SAS, a statistical package (acceptable to the FDA), which is used to provide the final tables, graphs, and statistical analyses. The CRO should provide a detailed analysis plan with examples of the statistical output (including the tables, listings, and graphs). Any programs or macros used should be fully validated (and not just quality controlled for accuracy). This statistical output

is made available to the project team and the client company and is used as the basis for writing the integrated safety report.

Bioanalytical Data

The bioanalytical work is usually straightforward, assuming that both the laboratory and the method were fully evaluated before dosing. Although this proactive due diligence is a necessary first step in assuring that this phase of the study will go smoothly, it should not be the only contact that the CRO has with the laboratory.

One critical area is the shipment of samples from the clinic to the laboratory. Whether the clinic is in another building at the CRO or whether the samples are being shipped to another location, nationally or internationally, it is imperative that the samples arrive at the analytical laboratory intact and frozen. Before any analyses, the CRO should conduct a detailed inspection and inventory of all samples. The samples should then be placed in a suitable freezer for storage until analysis takes place.

Study timelines are affected by the CRO's experience with the drug and/or metabolite and the ruggedness of the analytical method. In fact, outside of clinical recruitment and dosing, the bioanalytical phase of BA/BE studies often becomes the rate-limiting factor in the CRO's timeline. For this reason, it is usually essential that the analytical method be developed and validated before dosing. The unpredictability of assay development and validation timelines can have an adverse effect on the overall timeline if samples arrive at the laboratory before validation. However, some companies will evaluate the benefit/risk ratio before dosing without analytical validation. Their decision is based on their past experience with the CRO, the anticipated complexity of the assay and the potential for shortening the time to get their product to market. Generic companies will carry a substantial risk when working with a CRO that has not fully developed the analytical method. However, for Paragraph IV submissions, the benefit of being the first generic to submit an ANDA can outweigh this risk.

With the advent of high-throughput liquid chromatography-tandem mass spectrometry assays, the time required for bioanalysis can be substantially shortened. Although this is generally regarded positively, it can also have a negative impact (especially for those studies with limited sample volumes) if a problem goes undetected. Therefore, it is wise to reassess the sensitivity (limit of quantitation [LOQ]), specificity, and standard curve range after the first couple of analytical runs:

- Are all pre-dose sample concentration values reported as "BLQ," i.e., below the lower LOQ (LLOQ)?
- Is the chromatography "clean" and free of interfering peaks?
- For mass spectrometry assays, is there any indication of suppression?
- For single-dose studies, do the concentrations decrease to BLQ and remain undetectable? Or do the concentrations fluctuate between BLQ and measurable values?
- The calibration range should be reassessed.
- Is the LOQ too high or low?

- Is the top end of the range sufficiently high enough so that samples do not require dilution? Some CROs charge additional fees for diluting and reassaying samples exceeding the range of the calibration curve.
- Is the top end of the range too high? Perhaps the method was originally set up for a parenteral dosage form or for higher doses that might be needed for toxicokinetic studies. FDA reviewers have been known to question studies in which the majority of the sample concentrations fall within only the lower quarter to third of the calibration range.

Once this assessment is complete, the remaining samples can be assayed. Additionally, FDA requires that 5% to 10% of the samples be reanalyzed to assess incurred sample reproducibility (10% of the samples for studies with <1000 samples; 5% for studies with >1000 samples). Samples should be obtained around C_{max} and in the elimination phase and samples below the LOQ should not be selected.

This reanalysis of samples is required because the bioanalytical standards and QCs (made from commercial drug-free plasma, serum, or urine) may not be representative of study samples from dosed subjects (incurred samples). A number of factors can affect both the accuracy and precision of the concentration determined in incurred samples. These factors can include presence of metabolites converting to the parent species, protein binding differences, recovery issues, sample homogeneity, and mass spectrometric ionization matrix effects [9].

Upon completion of the entire data set, these data may again be evaluated for "aberrant data," that is, data that are pharmacokinetically uncharacteristic of the drug. The chromatography of these samples should be closely inspected. It is important that samples should not be reanalyzed without objective written criteria.

Before FDA submission, the bioanalytical package should be reviewed for common (and recurring) problems with BE submissions identified by OGD (http://www.fda.gov/downloads/Drugs/NewsEvents/UCM237460.pdf). These include the following:

- Electronic data tables are wrong or incomplete.
- Documented frozen storage stability is less than the time between the first sample blood draw and final sample analysis.
- Objective criteria and SOPs for pharmacokinetic repeat analyses are not provided.

Pharmacokinetic Analyses

As mentioned earlier, once the project specifications are known and the client has approved the proposal, the CRO should provide a detailed analysis plan. This detailed plan is generally unnecessary for a generic BE study because the analyses and report formats are straightforward and similar for most conventional BE study designs. For NDA-track BA studies, the analysis plan is relevant and it is important to have input from both the project pharmacokineticist and statistician. For these studies, the analysis plan provides details of the pharmacokinetic analyses and the statistical analyses of the safety data.

Pharmacokinetic analyses are usually conducted in accordance with CRO SOPs unless previously arranged by the client. This is important to note because some pharmaceutical companies insist that the CRO use their company's SOPs for pharmacokinetic analyses.

Noncompartmental pharmacokinetic parameters should to be calculated (using validated programs) based on final (QA-approved) bioanalytical data and actual sampling times. If interim pharmacokinetic analyses are necessary, it is usually adequate to conduct these analyses using preliminary analytical data and nominal sampling times.

Preparation and Review of the Final Report

The content and format of the final report was previously included in the overall project specifications. For example, the number and layout of in-text tables and graphs and the graphics software must be identified early and must be compatible with any client-specific report template.

When the data become available, the CRO team (consisting of the pharmacokineticist, statistician, and medical writer for NDA-track programs or only the pharmacokineticist for ANDA-track programs) and the client team should meet to discuss the study results. Usually, a teleconference will suffice. It is useful to include the client's project manager, pharmacokineticist, and statistician in these team meetings. This meeting provides an opportunity for the CRO to present and discuss any unusual observations (pharmacokinetic or statistical) that should be addressed in the report and it allows early input from the client team. Early client input allows for a consensus as to the clinical relevance of the pharmacokinetic results. The CRO can then use this discussion as a basis for writing the final report.

When reviewing integrated or pharmacokinetic reports, it is good practice for sponsors to consolidate all "internal" comments from each of their (the client's) reviewers. This consolidation is necessary because multiple client reviewers can (and often do) disagree on interpretation, format, and style. Timelines can be delayed if the CRO medical writer is required to negotiate changes across departments within the client organization.

EVALUATION OF THE DELIVERABLES

Once a study has been successfully concluded, the CRO will produce an integrated or pharmacokinetic report. If the CRO services were contracted to multiple CROs, then the sponsor (or one of the CROs) will need to integrate information from as many as three different reports or areas:

- A bioanalytical report that provides all details of the analytical method, validation, and the complete bioanalytical results including calibrators, QC values, and appropriate chromatograms
- A clinical report that provides the details of the clinical conduct and protocol deviations

- A final report (often a pharmacokinetic report) that integrates the clinical conduct, bioanalysis, pharmacokinetics, and statistics of the study into a concise report in a format suitable for submission to the FDA

Bioanalytical Report Checklist

The bioanalytical report should be assessed to confirm that it provides the required information on validation. Each analyte in each biological matrix must be validated with respect to sensitivity, selectivity, accuracy, precision, reproducibility, and stability. Table 12.4 provides a checklist that can be used to assist with this assessment.

Clinical Report Checklist

The clinical report should be assessed to confirm that it provides all of the information required by the FDA and the sponsoring company. Table 12.5 provides a checklist that can be used to assist with this assessment.

Integrated Pharmacokinetic Report Checklist

The integrated pharmacokinetic report (i.e., the final report) should be assessed to confirm that it provides all of the information required by the FDA and the sponsoring company. Table 12.6 provides a checklist that can be used to assist with this assessment.

WORKING TOGETHER WHEN A STUDY GIVES UNEXPECTED RESULTS

Because BA and BE studies include complex processes, it is not unusual for unanticipated "problems" to arise. However, clear and effective communications, appropriate planning, and willingness of both parties to identify and fix the problem can prevent most of these problems or issues. These problems can be as "simple" as missing expected timelines to as complex as failure to establish BE in a BE study. A number of issues and problems are discussed in the following sections.

Clinical

Recruitment Issues Delayed Study Timelines

Recruitment issues can lead to delayed clinical timelines and may result in analytical delays that can cause the overall study timeline to increase. Sponsors and CROs need to pay special attention to any protocol design issue that may affect the ability to recruit the target population. For example, if the sponsor insists on an exact 50/50 mix of males and females, then the CRO could have difficulty in recruiting the study as a single dosing group. As another example, recruitment could be an issue if a sponsor places a very narrow age range on an elderly subject population. In these

TABLE 12.4
Bioanalytical Validation and Report Assessment Checklist

Critical Area	Specific Area to Review	Check (✓)
Sensitivity	The validation report should define and validate the LLOQ.	
	Chromatography should be reviewed for potential interfering substances in a biological matrix and include endogenous matrix components, metabolites, and decomposition products that can affect the LLOQ.	
Selectivity	Selectivity is the ability of an analytical method to differentiate and quantify the analyte in the presence of other components in the sample.	
	If more than one analyte is required, then each analyte should be tested (in the presence of the others) to ensure that there is no interference.	
	Assay selectivity in the presence of any concomitant medications should be assessed.	
Accuracy	Accuracy should be measured using a minimum of five determinations per concentration.	
	The mean value should be within 15% of the actual value except at LLOQ, where it should not deviate by more than 20%.	
Precision	Does the report include data on the precision of the analytical method (describes the closeness of individual measures of an analyte when the procedure is applied repeatedly)?	
	Generally, the precision determined at each concentration level should be less than or equal to 15% (CV), except for the LLOQ, where it should not exceed 20% (CV). If not, is justification provided?	
Reproducibility	Does the report establish that the relationship between concentration and response of the analytical method? Is it linear?	
	Does the report demonstrate that the relationship between response and concentration is continuous and reproducible?	
Stability	Has freeze-thaw stability been assessed for three to five cycles and at least for the maximum number of times that any single sample in the study was thawed for reassay?	
	Has short-term temperature stability been assessed at room temperature?	
	Has long-term stability been assessed? The long-term stability duration should exceed the storage time between the date of first sample collection and the date of last sample analysis.	
	Does the report document stock solution stability? This is the stability of drug and the internal standard stock solutions that should be evaluated at room temperature for at least 6 hours.	
	Has the postpreparative stability been assessed? This is the stability of processed samples, including the resident time in the autosampler.	

(*continued*)

TABLE 12.4 (Continued)
Bioanalytical Validation and Report Assessment Checklist

Critical Area	Specific Area to Review	Check (✓)
Incurred Sample Reproducibility	Were 10% of the samples (5% for studies with >1000 samples) reanalyzed and assessed for reproducibility?	
	Were concentrations obtained for the initial analysis and reanalysis within 20% of their mean for at least 67% of the repeats? Were large differences between results (possibly indicating analytical issues) investigated?	
Additional Supportive Data	The report should include separate tables summarizing calibrators and QC values collected during the analysis of the study samples.	
	The report should include a table summarizing all repeat analyses with explanations and copies of all relevant SOPs.	
	The report should include example chromatograms. The FDA OGD requires 20% of the standard curve, QCs, and study samples to be submitted.	

cases, it is prudent for the client and CRO to discuss any recruitment issues early and to work closely during the "recruitment" phase so that there are no surprises.

Clinical Dropouts and Clinical "No-Shows"

Clinical dropouts and no-shows can affect the clinical completion date. The number of dropouts and no-shows should be anticipated by the CRO. Given this information (based on past studies) the CRO and sponsor should agree to recruit and dose additional subjects so that the required number to complete can be met. As above, the sponsor and CRO should stay in close communication during the planning phases to allow for this potential (but predictable) problem.

The clinical dropouts and no-shows can also have a significant effect on the outcome and validity of the study. It is critical that the protocol includes information as to the statistical treatment of data due to dropouts, the use of replacement and/or reserve subjects, and the bioanalysis of samples from dropouts, replacement, and/or reserve subjects. Several examples/issues follow.

A common result of a protocol that does not allow for the replacement of dropouts is a statistically nonbalanced study. Small differences in the number of subjects in each treatment (i.e., 1 or 2 out of a group of 12 to 18) will not usually have a statistically significant effect on a two-period (two treatment) BE study. This study design is usually robust enough to handle small differences in group sizes. However, larger numbers of dropouts can cause a significant sequence or subject-by-sequence effect. A statistically significant effect (due to an unbalanced design) can result in a "nonapprovable" BE study.

Protocols that allow replacement of dropouts can experience another problem that can potentially invalidate a biostudy. Some protocol designs allow "make-up" groups to be dosed if an insufficient number of subjects do not report for any one

TABLE 12.5
Clinical Study Report Checklist

Specific Area to Review	Check (✓)
Were there any protocol deviations?	
Did all subjects meet inclusion/exclusion criteria?	
If not, were the deviations clinically significant and did the principle investigator and client approve all deviations?	
Did the study recruit and dose the number of subjects required by the protocol?	
Were the appropriate number of men and women (where applicable) dosed?	
If not, are the reasons identified in the clinical report?	
Did all subjects complete all phases of the study?	
Are dropouts described?	
Was the study dosed as a single group?	
If not, are the reasons discussed in the report and did the client approve multiple dosing groups?	
Does the report include a demographics table identifying subject number, age, gender, weight, height, frame size, and smoker/nonsmoker status?	
Are all adverse events summarized in the report?	
Were any adverse events classified as serious and unexpected?	
Were these reported to the FDA within the required time interval?	
Did any subjects vomit at any time during the treatment phases?	
If so, are the dates and times relative to dosing recorded?	
Were all blood (and urine when appropriate) samples collected?	
Were all samples collected on time?	
If not, does the report identify missing samples (with reasons) and late/early blood and urine collections?	
Does the report include a physical description of the drug products, lot numbers, and expiration dates?	
Were the drug products administered in the fasting state (except for food effect studies) with 240 mL (8 ounces) of water?	
If not, is justification included in the report or protocol?	
Were subjects allowed to have water (ad libitum), except for 1 hour before and after drug administration?	
Was the washout period identical for all subjects (and groups, where applicable)?	
Were standardized meals provided no less than 4 hours after drug administration?	
Were meals identical in each phase of the study?	
Did the subjects abstain from alcohol for 24 hours before each study period and until after the last sample from each period was collected?	
Does the report provide a summary of dosing and the randomization (subject, sequence, period, and treatment)?	

TABLE 12.6
Integrated Pharmacokinetic Report Checklist

	Check (✓)
Is the study design appropriate?	
Does the pharmacokinetic report provide lot numbers, expiration dates, and potency values?	
Did the test and reference product potencies differ by no more than 5%?	
Were the appropriate moieties (analytes) measured (as defined in Section IV.B of the general BA/BE guidance)?	
Parent drug and major active metabolites for NDA BA studies	
Parent only for BE studies, unless the metabolite is formed as a result of gut wall or other presystemic metabolism	
Was blood sampling adequate to define the pharmacokinetics of the drug (and active metabolites)?	
12 to 18 samples including predose	
C_{max} should not be the first point	
3 to 4 samples should be obtained during the terminal log-linear phase	
Was the washout period adequate (≥5 times the half-life)?	
Were all pre-dose values less than LOQ?	
If not, were all pre-dose values ≤5% of each respective C_{max} value?	
Were all subjects with pre-dose values ≥5% of C_{max} dropped from all BE study calculations?	
First point C_{max}: Do any of the concentrations vs. time profiles exhibit first-point C_{max} (i.e., the first sample collected is the C_{max} value)?	
If so, were 3 to 5 samples collected within the first hour and was one of these collected between 5 and 15 minutes post-dose?	
If these early samples were collected, no change in data analysis is warranted.	
If these early samples were not collected, then those subjects with first point C_{max} values should be dropped from the primary statistical analysis.	
Did any adverse events (e.g., emesis) occur that would alter the drug pharmacokinetics?	
For immediate-release products, did any subject vomit at or before the median T_{max}? If so, were these subjects dropped from the analyses?	
For modified-release products, did any subject vomit at any time during the labeled dosing interval? If so, were these subjects dropped?	
Does the pharmacokinetic report provide the following information?	
Plasma concentrations and actual sampling time points	
Identification of subject, period, sequence, and treatment assignments	
Values for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, and half-life	
Subject by formulation interaction variance component (for individual BE [replicate design] studies)	
For steady-state studies: C_{min}, C_{avg}, degree of fluctuation, and % swing	
Partial AUC for drug products in which early exposure is important	
Geometric and arithmetic means, ratio of the means, and confidence intervals on log-transformed AUC and C_{max}	
Do confidence intervals fall between 80.00% and 125.00%?	

dosing period. The use of make-up groups can have disastrous consequences for a BE or BA study. As mentioned earlier, a statistical test for pool-ability of the data from these groups is required. If these make-up groups are unbalanced or small in number, then it is difficult to statistically prove pool-ability. If this occurs, then the data cannot be pooled and the result is often (or usually) an inability to establish BE.

The bioanalysis of samples from dropout subjects becomes a dilemma if not addressed in the protocol. Many companies specify (in the protocol) that only samples from subjects completing both (or all) periods of a study will be analyzed. The analysis of samples from "incomplete subjects" usually will not affect the statistical outcome of a study. However, an unbalanced study may affect the arithmetic mean data. Also, because the unbalanced data are of no use in establishing BE, it is not cost-effective to analyze these samples. Unfortunately, and unless stated in the protocol, the FDA generally expects to see all data generated from samples obtained in clinical trials.

A similar problem is encountered when dosing "reserve" subjects to assure completion of a minimum number of completers. If 28 subjects are dosed to complete 24 and all 28 complete both periods, then the company/CRO must "decide" which subjects (or how many subjects) to assay. This problem is alleviated if the protocol specifically addresses which subjects will have samples assayed (e.g., the first 12 subjects from each dosing sequence who complete both periods).

Dropout and/or replacement subjects can cause a number of potential problems; some of these problems can be trivial, whereas others can cause a study to "fail" FDA criteria. It is important to address these issues within the protocol; otherwise, the company/CRO will have to live with the consequences. While addressing these problems during the protocol development phase of the study, the company will need to come to terms with the financial implications of dosing replacement/reserve subjects (including the bioanalytical costs) as well as the moral implications of exposing more human subjects to an experimental drug and possibly discarding data from those subjects.

Unanticipated Adverse Events

Unanticipated adverse events, or a larger than expected number of adverse events, can affect the completion date for those studies that require a fixed number of subjects to complete all treatments. The sponsor and CRO should discuss the effect of adverse events (based on the drug class if there is no experience) on the dropout rate for the study. Although unanticipated adverse events are difficult to estimate, it is prudent to develop protocols that overestimate the dropout rate so that a sufficient number of subjects complete.

Dosing Errors

Dosing errors should not occur if the protocol is clearly written and the clinic follows the instructions. If dosing errors do occur, the credibility of the CRO clinic comes into question. The CRO should provide the results of an in-depth investigation together with a procedure to insure that the problem will not be repeated. If the problem was due to vague protocol instructions, then the CRO should address any questions before dosing.

Blood Collection Errors

Blood collection errors involving collection of the wrong time points or collection of blood using the wrong anticoagulant can occur. Analytical methods are usually developed for a particular matrix and additional validation may be required for matrix changes (e.g., plasma to serum and heparinized plasma vs. EDTA plasma). Although blood collection errors do occasionally occur, the problem may be due to conflicting instructions within the protocol. It is incumbent on the CRO to thoroughly read all sections of the protocol and to identify any discrepancies before clinical conduct.

Bioanalytical Issues

Most of these bioanalytical "problems" can be avoided if appropriate due diligence is provided before awarding the study or at least before dosing.

Validated Methods Not Reproducible under Clinical Condition

Bioanalytical methods are usually validated using five or six sources of "control" matrix (serum, plasma, etc.). However, this is often not sufficient to provide assurance that the assay will be sufficiently rugged to measure concentrations from 24 or more subjects. Sponsors should be cautious when awarding studies to a CRO with an "untested" or unvalidated analytical method. Experience is the key; unless timing is an issue, sponsors should assess validation packages and the CRO's experience.

Excessive Number of Rejected Runs

This becomes a problem when an excessive number of rejected runs affects analytical timelines. This problem is often indicative of an assay that is not rugged and has not been developed for studies with large numbers of samples. As above, lack of experience with the method should have indicated that the CRO might have a difficult time in meeting aggressive timelines. Sponsors should carefully assess the validation package for ruggedness and should include additional analytical time for those methods without a high experience level.

Number of Reassays Exceeds Freeze-Thaw Validation Cycles

Occasionally, the number of times that some samples are reassayed exceeds the number of freeze-thaw cycles included in the validation package. This is another indicator that an assay was not sufficiently rugged for routine clinical studies. If a CRO has to reassay samples several times (perhaps due to rejected runs), then the FDA will question the validity of the analytical method. Close communication between the sponsor and the CRO is required in this situation; the CRO should not finalize the analytical report until the validation report is supplemented to contain data that will support the additional freeze-thaw cycles.

Clinical Samples Arrive at Laboratory before Assay Validation

Study delays occur when clinical samples arrive at the laboratory before completion of assay development or validation. This is a problem that occurs most often when a sponsor is on a tight timeline and has provided a "dosing date" to their management.

It is unwise and risky to begin dosing a study while assay development or validation is still ongoing. It is usually best to delay dosing until the assay has been fully developed and validated.

Insufficient Long-Term Frozen Stability Data

Delays in assay validation can have additional trickle-down effects on the conduct of BA/BE studies. This can result in a report that provides insufficient long-term stability data necessary to support clinical trial sample stability. The FDA's bioanalytical guidance requires that drug companies and CROs include, in each report, long-term stability data that should exceed the time between the date of first sample collection and the date of last sample analysis. Clinical study delays may lengthen the storage time to beyond that in the validation report. However, most CROs will ship "spiked frozen controls" to the clinical site before dosing. These samples are stored with the samples from the clinical trial and are shipped back to the analytical laboratory upon completion of the trial. Assay of these control samples will provide the necessary long-term stability needed for the FDA approval. If these control samples were not prepared proactively, then the sponsor will have to accept a delayed timeline because the analytical report is not considered complete without these additional data.

Clinical Sample Matrix Different from Validated Matrix

This problem sometimes occurs when clinical protocols are not written specifically with regard to the anticoagulant. For example, if a protocol specified EDTA as the anticoagulant but the laboratory has validated the analytical method for heparinized plasma (using sodium heparin), then the laboratory will be required to conduct a "cross-validation" to establish that there is no matrix effect. This situation may occur when multiple CROs are involved in a single study. It is incumbent on the client to assure that the protocol contains the necessary collection and storage conditions that match the analytical validation.

LOQ Set Too High/Calibration Curve Range Not Appropriate

The LOQ is sometimes set inappropriately based on experience with alternative dosage strengths, dosage forms, or even based on preclinical experience. Similarly, the validated calibration range may be based on experience with higher doses. This problem can usually be avoided by obtaining advice from a pharmacokineticist from either the client company or the CRO.

Specificity Not Adequately Established

The FDA expects specificity to be established in the presence of metabolites and concomitant medications. All analytical methods should be validated in the presence of all known, major metabolites. Often, the metabolites are unknown during early Phase I studies on new chemical entities. However, once the metabolites are identified, the validation should be amended to contain the additional specificity data. Also, analytical methods should be validated in the presence of known over-the-counter (OTC) drugs. Usually, this is accomplished by testing a "cocktail" or mixture during validation. This is usually done as a precaution because BE studies

should be conducted in volunteers and in the absence of any concomitant medications. However, it is not unusual for one or two volunteers in a study to take an OTC drug product (e.g., ibuprofen or acetaminophen for headache relief). Once a clinical study is completed, the clinic should report all concomitant medications to the laboratory. The laboratory should include additional assay specificity data in the final analytical report.

Statistical (When a Study Fails)

Insufficient Subjects due to Adverse Events

Adverse events (such as emesis) can alter the number of subjects that can be included in the pharmacokinetic and statistical analysis. The FDA general BA/BE guidance is quite specific on how these events should be handled. It is extremely important that the project pharmacokineticist, the clinical and analytical project managers, and the client discuss the impact of these adverse events before completing the clinical conduct and/or the bioanalytical analyses. If these adverse events alter the number of "pharmacokinetically evaluable" subjects, then consideration should be given to amending the protocol (before assaying samples) to ensure that an adequate number of evaluable subjects (to yield statistical power) will complete the clinical phase of the study.

Statistical Issues: Power and Failed BE Study

It is important to maintain the statistical power of a study by ensuring that the required numbers of subjects complete the study. Often, though, statistical power is a secondary consideration. However, for generic BE studies, it is critical that an adequate number of subjects be dosed to meet the confidence interval criteria for BE. The inability to prove BE may be due to dosing too few subjects or to a true formulation difference. If the ratio of the means (for AUC or C_{max}) is close to unity, but the confidence intervals do not include the goalposts (usually 80% to 125%), then the solution may be to dose a new study with more subjects. However, if the ratio of the means is substantially different from 1.00, then the test formulation may indeed be bioinequivalent. At this point, the client should discuss these data with their drug product formulators.

Statistical Issues: Group Effects

Group effects are relevant only when a study is unable to dose as a single group. For example, if a CRO enrolls only 16 subjects (from a 24 subject study), then a "makeup group" is required. However, the FDA now requires that "pool-ability" be tested. A significant group effect often means that a BE study may fail to establish BE because the data from the two groups cannot be pooled and must be evaluated separately. The best solution is to avoid using multiple groups within BE studies by recruiting and dosing an adequate number of subjects to complete as a single dosing group.

FDA Preapproval Inspection of the CRO and FDA Form 483

It is not unusual for the FDA's Office of Compliance to "inspect" the clinical and analytical conduct of most generic BE studies for ANDA applications and to issue an

FDA Form 483. This form provides a listing of observations that are to be corrected. These observations can range from relatively minor observations to significant cGLP or cGCP violations. However, serious FDA 483's can usually be avoided by conducting a thorough due diligence assessment of the CRO before study assignment.

In the past, only major problems were listed on an FDA 483; however, today, even minor observations are being recorded. One of the keys to a successful study is to provide an acceptable and timely response to the Agency. The CRO should notify the client company of any FDA inspection at the time of the inspection and should provide a copy of the 483 to the client company. The CRO response to the 483 should be discussed with the client company before submitting the response to the Agency. Finally, when the response is submitted to the FDA, a copy should be provided to the client company.

SUMMARY

This chapter has provided a process for working with CROs to conduct BA or BE studies. The process began with an assessment of a number of CROs (and their capabilities) and included a due diligence inspection. It is critical to the process of working effectively with CROs that client companies (and the CRO) precisely define deliverables and expectations, assign a qualified project team, and develop communications systems that work for both the CRO and client company. If the client and CRO team members monitor and review deliverables and timelines, then there should be no surprises with regard to the timeliness and quality of the final deliverables.

Finally, it is worth emphasizing that the success of an outsourced clinical study is dependent on close collaboration and seamless communication between their organizations. This collaboration (partnership) requires open communication, sensitivity to project requirements and timelines, and flexibility on the part of both the CRO and client company that are necessary to achieve study success.

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13 Postapproval Changes and Postmarketing Reporting of Adverse Drug Experiences

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INTRODUCTION

Approval of an abbreviated new drug application (ANDA) is only the beginning of a generic drug product's history, as there are numerous postapproval requirements and activities to ensure that marketed drug products remain safe and effective. This chapter discusses a few of the important postapproval requirements from a regulatory affairs perspective.

Frequently, changes are made to the chemistry, manufacturing, and controls (CMC) section of an ANDA following approval and applicants are required to report these changes to the U.S. Food and Drug Administration (FDA). For example, an

ANDA applicant may make postapproval changes to the drug formulation, batch size, manufacturing process, equipment, or manufacturing site, just to name a few. These postapproval changes could potentially affect the identity, strength, quality, purity, and potency of the finished product and therefore must be fully evaluated before implementation to determine any impact on the finished product, as it may relate to safety or effectiveness. The potential for a change to have an adverse affect on the product determines how the change should be reported to the FDA (i.e., the type of submission) and when the change can be implemented.

The reporting of adverse drug experiences (ADEs) to the FDA is also discussed in this chapter. Although the reporting of adverse events is not a new concept to an ANDA applicant because it is required even for bioavailability or bioequivalence studies not performed under an investigational new drug [1], the process and requirements are somewhat different postmarketing.

Additionally, risk evaluation and mitigation strategies (REMS) and safety-related labeling changes are briefly touched on as part of the postapproval maintenance of a drug product.

CMC POSTAPPROVAL CHANGES

Changes to an approved ANDA can be initiated for a number of business or manufacturing reasons including, but not limited to, the following: revised market forecast affecting batch size requirements, qualification of a new active pharmaceutical ingredient (API) source, optimization of the manufacturing process, upgrade of the container closure system, or improvements to the analytical test methods. A change within a given parameter can have varied potential adverse effects depending on the type or dosage form of the product. For example, a change in the container closure system of a solid oral dosage form will have less impact on the drug product than it would for a semisolid or oral liquid dosage form, where the primary packaging component becomes critical for the shelf life of the finished product. To illustrate further, a small change in the concentration ratio of an inactive ingredient may have less impact on an immediate-release drug product than it would for a modified-release product, where that same ingredient may affect the release rate, thereby impacting bioequivalence. Under such circumstances, the reporting requirements for one will differ from those for the other depending on the dosage form and route of administration.

Single or multiple changes within the same ANDA over time can have an impact and must be considered in the overall life of the drug product as well. Numerous changes to the manufacturing parameters occurring over time may render the drug product approved in the original ANDA substantially different than the one on the market. Therefore, data submitted in an application to support most changes should include a comparison with the original exhibit batch or biobatch wherever possible [2].

History of the Regulations and Guidances

There are laws, regulations, and guidances relating to making CMC postapproval changes. Before 1997, postapproval CMC changes were regulated by 21 CFR 314.70 *Supplements and Other Changes to an Approved Application*, which was vague and

left room for inconsistent interpretation by both the industry and the FDA. Beyond the CFR, the FDA issued the *Guidance for Industry: Immediate Release Solid Oral Dosage Forms—Scale-Up and Postapproval Changes* (SUPAC-IR) to provide the industry with clear and definitive language regarding the regulatory notification process and requirements for postapproval changes [3]. The guidance also attempted to reduce the regulatory burden for the industry and its issuance was a major milestone for the pharmaceutical industry. SUPAC-IR categorizes changes by levels and the criteria for these levels and the documentation required to support the changes were based on three independent studies: (a) research conducted by the University of Maryland in association with the FDA; (b) results from a workshop among the American Association Pharmaceutical Scientists, U.S. Pharmaceutical Convention, and the FDA; and (c) research conducted at the University of Michigan and the University of Uppsala. Although much of the information in SUPAC-IR has been superseded by subsequent guidances, it is still referred to for some changes, including those to the components and composition of a drug product.

On November 21, 1997, the FDA Modernization Act was signed into law and provided specific language for manufacturing changes to an approved application as well as the associated reporting requirements for those changes. In 1999, the original 21 CFR 314.70 expired and the FDA issued an interim guidance document, *Guidance for Industry: Changes to an Approved NDA or ANDA* (CANA), which became the reference for determining the appropriate postapproval regulatory submission for CMC changes [4]. A revised version of both 21 CFR 314.70 and the CANA guidance became effective in 2004. In addition to this specific regulation and guidance document, which provide for the type of postapproval submissions, many other guidance documents have been issued providing further direction regarding filing categories as well as the data and information required to support CMC postapproval changes. The pharmaceutical industry and its regulation are constantly evolving as demonstrated recently by initiatives like Quality by Design and risk-based approaches, and the FDA attempts to address this evolution through revising existing guidances and issuing new guidance documents. Therefore, it is important for applicants to stay current with the FDA's publications and expectations.

Types of CMC Postapproval Regulatory Submissions

The CANA Guidance and revised 21 CFR 314.70 provide for four types of CMC postapproval submissions [2]. The type of reporting category is relative to the "potential" risk or adverse impact the change could have on the identity, strength, quality, purity, or potency of the product as they may relate to its safety or effectiveness. These postapproval regulations apply to changes made to the API as well as to the drug product. Tables 13.1 and 13.2 list the submission categories with examples of the types of changes that fall into each category for the drug product and API, respectively. The types of submissions are discussed in more detail following the tables.

An applicant is required to assess the impact of all proposed changes on the API and/or product. For example, if an applicant is making a change in the API, not only do they need to demonstrate there is no adverse impact on the drug substance but they also need to demonstrate that the changed API does not adversely affect the drug product. In addition to ensuring that the API and/or product affected by the

change continues to meet specifications, an assessment may also include additional tests evaluating any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. If the assessment concludes that there is an adverse affect on the product and the applicant still wants to move forward with the change, they must submit a Prior Approval Supplement (PAS) regardless of the recommended reporting category [2].

TABLE 13.1
Types of CMC Postapproval Submissions and Example Changes for Drug Products

Type of Submission/ Filing Category	Potential Impact on Product	Example of CMC Postapproval Changes [2]	
		General Change Listed in Guidance	Specific Example
PAS	Substantial	Changes in technical grade and/or specifications of release controlling excipients in a modified-release solid oral dosage form [5].	Changing from Eudragit RS-100 to Eudragit RL-100.
		Changes in excipients, expressed as percent (w/w) of total formulation [3,5]. Refer to the guidances for specific percentages that require PAS.	Increasing the talc content by 1% (w/w) or more of the total formulation for a solid oral dosage form.
Supplement-Changes Being Effected (CBE) in 30 Days	Moderate	Reduction of an expiration dating period [2].	Reducing the shelf-life of your product from 36 to 24 months.
Supplement-CBE	Moderate	An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess [2].	Adding a new impurity to the specification with the associated test method and acceptance criterion.
Annual Report	Low	Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product [2].	Changing the color of a tablet by deleting the ingredient in the coating that provides the color (e.g., change in formulation of Opadry coating that eliminates the color ingredient).
		A change in the size and/or shape of a container for a nonsterile solid dosage form [2].	Changing from a 50 cc HDPE bottle to a 60 cc HDPE bottle.

TABLE 13.2
Types of CMC Postapproval Submissions and Example Changes for APIs

Type of Submission/ Filing Category	Potential Impact on Product	Example of CMC Postapproval Changes [2]	
		General Change Listed in Guidance	Specific Example
PAS	Substantial	Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties [2].	Changing solvents used in the synthesis of the API.
		Change to a new API supplier without extensive knowledge of the new and old sources (e.g., access to the drug master files). In this situation, an applicant cannot adequately describe the differences between the sources or evaluate possible related changes [6].	Changing API sources when the applicant does not have access to the Drug Master File to assess all of the changes and how they affect the drug substance.
Supplement-CBE in 30 Days	Moderate	Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements [2].	Updating the API impurity specifications to comply with an official compendium (e.g., USP) when it involves relaxing the limit.
Supplement-CBE	Moderate	A move to a different manufacturing site for the manufacture or processing of the final intermediate [2].	Changing suppliers or manufacturers of the final intermediate for the API.
Annual Report	Low	Tightening of an existing acceptance criterion [7].	Changing the existing specification limit for Impurity X from not more than 0.2% to not more than 0.1%.

Prior Approval Supplements (PAS)

A PAS is required when the proposed CMC change has a substantial potential to have an adverse effect on the product. With the submission of a PAS, the applicant must receive approval from the FDA before implementing the proposed change. Unlike branded drugs, where the FDA has specific review goals through the Prescription Drug User Fee Act (PDUFA) (e.g., review 90% of PAS within 4 months), generic drugs currently do not have review goal timings, so it is difficult to plan implementation when prior approval is needed. However, if a delay in approval of your PAS would cause a drug shortage or extraordinary hardship on the applicant, there is an

option to request expedited review of your supplement in accordance with 21 CFR 314.70(b)(4) [8]. Additionally, the Generic Drug User Fee Act (GDUFA), a current topic with the FDA and industry that is also discussed later in this chapter, could be enacted as soon as October 1, 2012 and would include future FDA review goals for PAS submitted to ANDAs [9].

Changes Being Effected (CBE) Supplements

A CBE Supplement is required when the proposed CMC change has a moderate potential to have an adverse effect on the product. There are two types of these supplements: Supplement-CBE in 30 Days (CBE-30) and Supplement-CBE (CBE or CBE-0).

After submitting a CBE-30 Supplement, if the applicant has not heard otherwise from the FDA, they may distribute product incorporating the proposed change 30 days after the FDA has received the submission. This 30-day waiting period allows the FDA to determine whether the necessary information to assess the change is provided in the supplement. If during the 30 days the FDA notifies the applicant that information is missing, distribution must be delayed until the missing information is submitted. On the other hand, the CBE-0 does not have this 30-day waiting period and the product may be distributed once the FDA receives the submission. Although implementation of the change may occur before formal FDA approval, both types of CBE supplements do undergo the review and approval process by the FDA.

Annual Reports

In accordance with 21 CFR 314.81(b)(2), an Annual Report should be submitted each year within 60 days of the anniversary of the approval date for the original application [10]. Minor CMC changes, which have a low potential to adversely affect the product, can be implemented after assessment and should be included in this yearly postmarketing report. Although the changes included in the Annual Report are considered minor, they still require an assessment of any potential impact they might have on the product and the associated data package should be included in the Annual Report. Additionally, data from required ongoing stability studies are submitted in the Annual Report. Although annual reports do not undergo a formal approval process such as supplements, the FDA does have the authority to request additional supportive information for a change. Furthermore, if the FDA disagrees with the Annual Report filing category for a specific change, they can require an applicant to file a supplemental application.

CMC Postapproval Regulatory Process

The CMC postapproval regulatory process actually begins with change control, which is required by cGMPs in 21 CFR 211.180(e) [4]. In addition to quality personnel and those from other affected areas, CMC Regulatory must assess whether the changes that the manufacturing site is proposing have any NDA or ANDA implications. The change control system should be well defined and controlled as it is fundamental not only to the CMC postapproval regulatory process but also to other business areas, such as validation, labeling, and quality assurance.

It is essential for Regulatory to fully understand the change to properly assess it, which frequently requires direct interaction with the manufacturing site. It is also common to find that there are multiple related changes. For example, an initial change control may propose to change manufacturing sites for a solid oral dosage form with no other changes. This type of change would require a CBE-30 [2]. However, upon discussion with the current and proposed sites, Regulatory may discover that the new site is changing from a wet to dry granulation, which requires a PAS [2]. The CANA guidance states that multiple related changes should be filed using the more restrictive reporting category. In this multiple related changes example, the reporting category changes from a CBE-30, where the applicant could possibly have implemented the site transfer 30 days after FDA receipt, to a PAS where the applicant must wait for FDA approval.

Once Regulatory understands the specifics of the proposed change, they can determine the appropriate filing category using 21 CFR 314.70 and the multiple guidances the FDA has issued. In addition to the submission category, Regulatory needs to provide advice as to what data and information the site needs to generate to be included in the submission. Table 13.3 provides a partial list of final and draft guidances the FDA has issued to assist industry in determining both the filing category

TABLE 13.3
Partial List of FDA Guidances Pertaining to CMC Postapproval Changes

Guidance Title	Type of Guidance Provided
Guidance for Industry: Changes to an Approved NDA or ANDA (CANA) [2]	Filing category
Guidance for Industry: Immediate Release Solid Oral Dosage Forms—Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (SUPAC-IR) [3]	Data and information, filing category
Guidance for Industry: SUPAC-MR Modified Release Solid Oral Dosage Forms—Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation [5]	Data and information, filing category
Draft Guidance for Industry: CMC Postapproval Manufacturing Changes Reportable in Annual Reports [7]	Filing category
Guidance for Industry: SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum [11]	Filing category
Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms [12]	Data and information
Draft Guidance for Industry: Comparability Protocols—Chemistry, Manufacturing, and Controls Information [13]	Data and information, filing category

Note: Ensure guidances have not been superseded by other guidances subsequently issued. For example, CANA supersedes SUPAC-IR concerning filing category guidance, but SUPAC-IR is still referenced for some data requirements and specifics around changes to Components and Composition.

and the supportive data package for solid oral dosage forms. Some of the required data may already be part of any validation or site assessment that is planned from a quality perspective, but some may not overlap and the regulatory requirements need to be communicated to the manufacturing site. This communication is all part of a successful and effective change control system.

Once the required data and information are gathered, the appropriate supplemental application is written and submitted to the FDA. During review, the FDA may have questions or request additional information. As discussed above, timing for implementing the change is dependent on which type of supplemental filing is submitted and whether prior approval by FDA is required.

Comparability Protocols

Comparability protocols are provided for in 21 CFR 314.70(e) and are discussed briefly in the CANA guidance. Additionally, the FDA published a draft guidance in 2003, *Guidance for Industry Comparability Protocols—Chemistry, Manufacturing, and Controls Information*, to provide recommendations on preparing and using comparability protocols for CMC postapproval changes [13]. According to the guidance, "A comparability protocol is a well defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including analytical procedures that will be used, and acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product."

A comparability protocol may be submitted with an original ANDA or NDA or postapproval as a PAS. One of the potential benefits of an approved comparability protocol is a reduced reporting category (e.g., CBE-30 instead of a PAS) for future CMC postapproval changes covered by the protocol, which could allow the applicant to implement changes sooner. Also, with an approved comparability protocol, the FDA is less likely to request additional information during review because they have already agreed to the data and information needed to support a specific change. Filing a comparability protocol can be a useful strategy, especially when an applicant expects to make the same type of change on multiple occasions and/or to multiple products.

POSTMARKETING REPORTING OF ADVERSE DRUG EXPERIENCES (ADEs)

Once the FDA approves a drug product, applicants are responsible for conducting postmarketing surveillance in accordance with 21 CFR 314.80 and 21 CFR 314.98 [14,15]. The main component of this requirement is the reporting of ADEs. According to 21 CFR 314.80(a), an ADE is defined as "any adverse event associated with the use of a drug in humans, whether or not considered drug related" [14]. The definition continues by stating that adverse events include those that occur in the course of the use of a drug product in professional practice, occur from drug overdose (accidental

or intentional), abuse, or withdrawal, or involve failure of expected pharmacologic action. According to the definition, it is irrelevant whether or not an event is considered drug related. Additionally, a known or proven cause-and-effect relationship between the drug and the event is not required. The fact that an adverse event occurred while a person was using a drug product is reason enough to consider it an ADE.

It is important to examine who is involved in the process of ADE reporting. Generally, there are three members that take part in this process: a reporter, an applicant, and the FDA. Essentially anyone can report an ADE. The "reporter" can be a patient, doctor, pharmacist, nurse, or anyone else aware of such an event. This person can report it to either the ANDA applicant or directly to the FDA. If the applicant receives the report first, the applicant is responsible for investigating the ADE and reporting it to the FDA. If the FDA is notified directly by the reporter, the Agency informs the applicant so that the ADE can be investigated. Part of investigating an ADE may include, but is not limited to, contacting the patient's physician, the prescriber (if different from the physician), and the pharmacy that filled the prescription. Other investigations include performing all required testings of the retain sample from the lot of the product that was used by the patient. Of course, there are many times when the lot number is not known; therefore, this testing cannot be conducted. Once an investigation is complete, the applicant is responsible for submitting the information in a report to the FDA.

Types of ADEs

After an adverse event is reported to an applicant, two classifications must be made. First, the adverse event must be categorized as either serious or nonserious. Second, it must be determined whether the ADE is expected or unexpected. Again, these terms are defined in 21 CFR 314.80. A serious ADE is "any ADE occurring at any dose that results in any of the following outcomes: death, a life-threatening ADE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect." In addition, the regulations include an "important medical event" that may endanger the patient and may require medical involvement to prevent one of the outcomes listed above. A nonserious ADE is one that does not result in any outcome listed in the definition of a serious ADE.

In regards to the expected and unexpected designation, the labeling of the product is used to determine the type of ADE. If the product labeling lists a particular adverse event, it is considered expected. If not, it is considered unexpected. However, this classification of ADEs is not always clear. Unexpected ADEs also include events that may be symptomatically and pathophysiologically related to an event listed in the labeling but differ from the event because of greater severity or specificity. For example, if a report is received that a patient experienced complete loss of vision while using a marketed product and the labeling of the product lists visual disturbances in the adverse effects section, the applicant may consider this an expected event. However, because complete loss of vision is more severe than the description in the labeling, this ADE would be classified as unexpected rather than expected. The key here is that applicants should not give the FDA the impression that reports or details of reports are being hidden or glossed over.

Reporting ADEs

It is important to correctly classify an ADE as either serious or nonserious and either expected or unexpected because the classification will determine the type of report that is submitted to the FDA. ADEs that are considered both serious and unexpected must be submitted to the FDA in an expedited manner and are known as "15-Day Alert Reports." Applicants must submit these reports to the FDA as soon as possible but in no case later than 15 calendar days of the initial receipt of the information. All other ADEs (those that are serious and expected, nonserious and expected, or nonserious and unexpected) should be reported to the FDA as Periodic Reports. Periodic Reports must be submitted at quarterly intervals for 3 years from the date of FDA approval of the product and then annually. Table 13.4 summarizes these requirements. Any follow-up information received after the initial submission to the FDA should be submitted to the FDA and should follow the same rules depending on whether the original ADE report was classified as a 15-Day Alert Report or Periodic Report. As discussed earlier, by submitting an ADE report to the FDA, applicants are simply notifying the FDA and not admitting guilt or even agreeing that the product caused the event.

There is certain information that must be known, though, before a report is submitted to the FDA. Among this information are four elements: an identifiable patient, an identifiable reporter, a suspect drug/biological product, and an adverse event or fatal outcome. If any of these basic elements remain unknown after being actively sought by the applicant, a report on the incident should not be submitted to the FDA, because reports without this information make interpretation of their significance difficult, if not impossible. In these cases, the applicant should track the steps taken to acquire the additional information in their safety files for the product [16].

To facilitate the reporting process, the FDA created the MedWatch program, which is the FDA Medical Products Reporting Program [17]. It was originally designed to emphasize the responsibility of healthcare providers to identify and report ADEs. Through the MedWatch program, healthcare professionals can report ADEs with the use of FDA Form 3500 (MedWatch Form). However, this reporting is done on a voluntary basis, as there currently are no regulations that require healthcare professionals to report ADEs to the FDA or the applicant. In contrast,

TABLE 13.4
Types and Timings of ADE Reports

Type of ADE Reported to Applicant	Type of Report Filed to FDA	Timing for Reporting to FDA
Serious and unexpected	15-Day Alert Report 15-Day Alert Report—Follow-up	No later than 15 calendar days of initial receipt of information
Serious and expected Nonserious and expected Nonserious and unexpected	Periodic Report	Quarterly intervals for 3 years from the date of ANDA approval then annually

an applicant aware of an ADE is required by law to report it to the FDA (provided the four elements noted earlier are known). The FDA/MedWatch Form 3500A is used for mandatory reporting by applicants. It is interesting to point out that, on the bottom portion of both MedWatch forms, there is a note that reads: "Submission of report does not constitute an admission that the product caused or contributed to the event." This is a reiteration of what was stated earlier in the CFR definition of an ADE.

During the investigation and submission of the ADE report to the FDA, patient privacy should be maintained. The applicant should not identify patients by name or address in the reports. Instead, the applicant should assign a unique code (e.g., patient's initials or a tracking number) to each report. In addition, names of patients, healthcare professionals, hospitals, and geographical identifiers in ADE reports are not releasable to the public under the FDA's public information regulations.

Although there is some complexity at times, the ADE reporting system is efficient and straightforward. The main goal of the requirement is to identify new or previously unrecognized adverse events that are caused by drug products. This often results in the addition of safety information to a product's labeling but can also lead to more severe actions such as product recalls or withdrawals. In any case, the objective is to expand the information available to the medical community and the public regarding a product's adverse event profile and therefore increase public safety.

RISK EVALUATION AND MITIGATION STRATEGIES

The original approved labeling for a drug product can change after FDA approval and subsequent marketing of a drug product. The FDA Amendments Act of 2007 gave the FDA the authority to require a REMS from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks [18]. The REMS program allows the FDA to conduct ongoing pharmacovigilance at any time throughout the product life-cycle. REMS hold sponsors responsible for assessing and monitoring specific risks, additional requirements, and responsibilities for stakeholders. REMS are required for NDAs, ANDAs, and biological license applications.

The FDA can require safety-related labeling changes based on new safety information that becomes available after approval of the drug or biological product. In this regard, the FDA can require the development of safety-related changes to a Medication Guide and can require these to be completed quickly whether or not a Medication Guide is part of a REMS. Medication Guides are part of labeling (21 CFR 201.57(c)) and are subject to the safety labeling change provisions of Section 505(o)(4) of the FD&C Act, added by the FDA Administration Amendments. Under these provisions, the FDA can require the development of a Medication Guide (or safety-related changes to an existing Medication Guide) based on new safety information of which the FDA becomes aware after approval of the product. Section 505(o)(4) includes tight timeframes for applicant submission of a supplement containing the labeling changes or a statement detailing the reasons why such a change is not warranted as well as authority for the FDA to order the labeling changes if agreement is not reached within the statutorily specified timeframes.

The FDA uses a Medication Guide to determine if one or more of the following circumstances exist:

1. The drug product is one for which patient labeling could help prevent serious adverse effects.
2. The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, the product.
3. The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

A "black box" warning is the most serious warning placed in the labeling of a prescription medication. Advertisements that serve to remind healthcare professionals of a product's availability (so-called "reminder ads") are not allowed for products with black box warnings. The new warning language does not prohibit the use of the drug in patients. The black box warning warns of serious risks related to drug use and encourages prescribers to balance this risk with clinical need.

TOPICS IN THE SPOTLIGHT

Although topics may change, there are always issues that have the focus of both the FDA and the industry. Two of these issues that affect the postapproval stage of a drug product are discussed below.

Generic Drug User Fee Act

There is currently a backlog of ANDA submissions and supplemental applications at the FDA leading to increased review and approval times. Although NDAs and associated supplements have the PDUFA, which requires applicants to pay a fee when filing NDAs and holds the FDA to specific review metrics, ANDAs for generic drugs do not currently have a similar program in place. However, the GDUFA is expected to be approved by Congress and made effective by October 1, 2012 [9]. Regarding postapproval activities, GDUFA will require an applicant fee when filing a PAS as well as provide the FDA review goals for these supplements. An example of an FDA review metric from the proposed GDUFA is as follows:

> FDA will review and act on 60 percent of PASs not requiring inspection within 6 months from the date of submission for receipts in FY 2015; FDA will review and act on 60 percent of PASs requiring inspection within 10 months from the date of submission for receipts in FY 2015 [9].

Although this program will institute fees for generic drug applicants, it will improve the predictability and timeliness of the review and approval process. This will ultimately allow applicants to better plan implementation of postapproval changes that require prior approval.

Drug Shortages

Drug shortages, especially when the drug is medically critical, can cause serious public health concerns. The subject of drug shortages has received much more publicity recently ranging from an Executive Order issued by President Obama on October 31, 2011 to the amendment of regulations through the Interim Final Rule (IFR) *Applications for Food and Drug Administration Approval to Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance* issued on December 19, 2011 (effective January 18, 2012) [19]. Although recent information shows that the majority of drug shortages are around sterile injectables (132 out of 178 shortages in 2010), the heightened scrutiny and changing regulations affect all drug manufacturers [20]. For example, before the recent IFR and the new *Draft Guidance for Industry Notification to FDA of Issues That May Result in a Prescription Drug or Biological Product Shortage*, sole manufacturers were required by 21 CFR 314.81 to notify the FDA at least 6 months before discontinuing a drug if the product was life supporting, life sustaining, or intended for use in the prevention of a serious disease or condition and was not originally derived from human tissue and replaced by a recombinant product. The IFR and guidance not only clarify "sole manufacturer" but also redefine "discontinuance" to include both temporary and permanent disruptions in supply of the drug product [19,21]. The IFR, guidance, and heightened scrutiny place more responsibility on the manufacturers and will hopefully provide the FDA's Drug Shortage Program with more lead time and information to help mitigate drug shortages.

CONCLUSION

Although initial approval of an ANDA is definitely an accomplishment and is understandably a priority of an applicant, there is a life cycle associated with each drug product and postapproval is a large and important stage of this life cycle. As discussed, the responsibility of an applicant does not end with approval of an ANDA—the focus simply changes postapproval to ensuring approved drug products "remain" safe and effective and "accessible" to the public.

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14 The United States Pharmacopeia/ National Formulary
Its History, Organization, and Role in Harmonization

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INTRODUCTION AND HISTORICAL BACKGROUND OF US PHARMACOPEIA

Today's global pharmaceutical industry arose from individual practitioners compounding their own medications. In 1820, a group of American physicians concerned with the quality and consistency of medicines created the *U.S. Pharmacopeia* (*USP*), essentially a book of recipes for commonly used medicinal preparations (Figure 14.1) [1]. Over time, the USP Convention evolved, both as a publication and as an organization, in parallel with the emerging pharmaceutical industry that largely took the place of individual compounders. In a 1950 edition of the *Bulletin of the World Health Organization*, Dr. George Urdang published an influential paper on "The Development of Pharmacopeias" [2]. Dr. Urdang was a distinguished professor of pharmacy at the University of Wisconsin and also was a driving force in the development of the USP into a modern, global public health organization. Dr. Urdang defined a pharmacopeia as "a compilation intended to secure uniformity in medicinal agents as to kind, quality, composition, and therapeutic strength, whose specifications are legally obligatory within a defined political area" [3]. For nearly a century, USP's drug standards have met that definition in the United States, and USP standards also are in used in more than 145 countries.

Starting as a collection of simples (drugs that had not been prepared by processes more involved than comminution or purification) [3] and formulas for compounding, *USP* evolved to include the physical attributes and chemical properties for the articles. Until the early 20th century, the articles included in the *USP* were characterized as officinal or necessary to the practice of medicine and were viewed as

FIGURE 14.1 Founding of the USP: The First General Convention, Washington, DC, 1820.

representing the best and most useful remedies (although this varied from state to state). In contrast, the *National Formulary* (*NF*) was first published in 1888 by the American Pharmacists Association (APhA) with the original objective of providing standards for unofficinal preparations (made extemporaneously upon demand but not kept on hand) [4].

Over the next 90 years, the contents of *USP* and *NF* were intertwined, with some articles moving several times between the *USP* and the *NF* depending on whether they meet the status conferred by *USP* as "most fully established and best understood." This system was manageable when *USP* was published on a 10-year cycle, as there was plenty of time for members of the USP and the APhA to meet and decide which monographs belonged in which compendium; however, after *USP* adopted a 5-year revision cycle, it became increasingly difficult to coordinate the publication and scope of each compendium. After lengthy discussions beginning in the 1970s, the USP eventually purchased *NF* from the APhA in 1975 and began publishing the joint *USP–NF* compendia in 1980. *USP* is now in its 36th edition; *NF* is in its 31th edition (represented as *USP 36–NF 31*).

Legal recognition in the United States for the *USP* as a source for standards for strength and purity dates from the 1848 Drug Importation Act. The 1906 Pure Food and Drugs Act gave force of law to the requirement that drugs sold under or by a name recognized in *USP* or *NF* meet the standards for identity, strength, and purity therein. *USP* and *NF* gained official status by their inclusion under the definition of "official compendium" in the 1938 Federal Food, Drug, and Cosmetic Act (FDCA). Under the FDCA, products marketed in the United States can be found to be adulterated or misbranded by evaluation against the various applicable standards given in *USP–NF*. The use of the standards in *USP* and *NF* continue to serve as sources of established names, packaging, and labeling information by which a product or substance can be determined to be misbranded [5] and provide assessments of strength, quality, and purity against which a product or drug substance can be judged as adulterated [6].

USP OVERVIEW: CONTENT AND PROCESSES

Scope of the Publications: *USP* and *NF*

Over its history, *USP* maintained its content as a guide to the drugs of medical choice, admitting drugs where usefulness was accepted by physicians. Thus, official articles populated the first rank in the physician's armamentarium. The articles in *USP* included simples as well as preparations. The original scope of the *NF* were formulas that could be compounded on a small scale by the pharmacist, and it referenced *USP* ingredients. With improvements in analytical sciences in the late 19th century, both publications began including physical attributes and where possible chemical properties. In 1916, *NF IV* included a new section with monographs for simple ingredients if such details were not already provided within *USP*. By the mid-20th century, the contents of the two publications were markedly similar in style and approach. When both publications came under the authority of USP, a rational division of content between the two compendia brought active substances and preparations within the *USP* and collected the excipient materials in *NF* in the combined publication.

The scope of *USP* was enlarged by Resolution No. 5 from the 1990 Convention to "expand the USP program for developing public standards and information for practitioners and consumers for vitamins and minerals used as dietary supplements and for enteral purposes" [7]. Standards for dietary supplements constituted approximately 7% of the text for *USP 34–NF 29*. The standards for vitamin and mineral supplements as well as botanicals are cited under the Misbranded Supplements section within the Dietary Supplement Health and Education Act (DSHEA) of 1994 [8]. That Act amended the 1938 FDCA. Where a dietary supplement is represented by a monograph, a product purporting to conform to the monograph can be found to be misbranded if it is found to fail to conform. It should be noted that, in the case of DSHEA, the product must represent itself as conforming to the monograph to be subject to the provisions in the Act. This more voluntary requirement contrasts with the situation for drugs, for which conformance is expected for any product whether or not a claim of conformance is made. USP also publishes the *Dietary Supplements Compendium* (*DSC*). The *DSC* contains information of use to dietary supplements manufacturers abstracted from *USP–NF*, and USP's compendium of quality standards for food ingredients, the *Food Chemicals Codex*.

USP Governance, Standards-Setting, and Advisory Bodies

USP's governance, standards-setting, and advisory bodies include the USP Convention, the Board of Trustees, the Council of Experts and its Expert Committees—all comprising volunteer members—and paid USP staff. Additional volunteer bodies include stakeholder forums, project teams, and advisory panels and groups, which act in an advisory capacity to provide input to USP's governance, standards-setting, and management bodies.

USP Convention

The composition of the USP Convention membership is designed to ensure a global representation from all sectors of healthcare, with an emphasis on practitioners, given USP's practitioner heritage. Voting delegates of convention member organizations elect USP's President, Treasurer, other members of the Board of Trustees, and the Council of Experts. They also adopt resolutions to guide USP's strategic direction and amend USP's Bylaws. Although frequency has varied over USP's existence, the current cycle calls for the Convention meeting to be held every 5 years.

USP Board of Trustees

USP's Board of Trustees is responsible for the management of the business affairs, finances, and property of USP. During its 5-year term, the Board defines USP's strategic direction through its key policy and operational decisions.

USP Council of Experts

The Council of Experts is the standards-setting body of USP. For the 2010 to 2015 cycle, it comprises 24 members, elected to 5-year term by the USP Convention, each of whom chairs an Expert Committee. These chairs in turn elect the members of their Expert Committees. The Expert Committees are responsible for the content of USP's official

and authorized publications. The Executive Committee of the Council of Experts includes all Expert Committee chairs and provides overall direction, is an appeals body, and performs other functions that support the Council of Experts' operations.

Expert Panels to the Council of Experts

The Chair of the Council of Experts may appoint expert panels to assist the Council of Experts by providing advisory recommendations to particular Expert Committees in response to a specific charge consistent with the Expert Committee's work plan. Expert panels are continuously formed or dissolved on an as-needed basis.

Stakeholder Forums and Project Teams

USP has formed several domestic and international stakeholder forums and project teams to exchange information on USP's standards-setting activities. Stakeholder forums may form project teams to work on selected topics [9].

USP's Role in Established Drug Names

On June 15, 1961, the American Medical Association–USP Nomenclature Committee was formed. This committee evolved into the U.S. Adopted Names (USAN) Council in January 1964 through the sponsorship of the USP, the American Medical Association, and the American Pharmaceutical Association. Its purpose was to institute an orderly and effective system for selecting nonproprietary names for new drug substances and certain other related agents. The 1962 Kefauver-Harris Amendments to the FDCA placed responsibility for the official names for drugs on the Secretary of Health, Education and Welfare (now Health and Human Services) [10]. In 1967, the U.S. Food and Drug Administration (FDA) joined the USAN Council as a means of consolidating the work of selecting suitable nonproprietary names for drugs on behalf of the federal government with the work of the council. Currently, the FDA generally defers to the USP to create nonproprietary names for drug products and to determine proper names for biologics; oversight of proprietary names remains the responsibility of the FDA, working with applicants.

The USP Nomenclature Expert Committee was established in 1985 to work closely with the USAN Council to determine established names for drug products. During the 2010 to 2015 USP Convention cycle, the Nomenclature, Safety and Labeling Expert Committee, which includes the FDA liaisons from many areas within the FDA, is expected to address mutual topics of interest to both USP and the FDA. The *USP Dictionary of USAN and International Drug Names* provides a reference for nonproprietary drug names and chemical structures [11].

Content of *USP–NF*

USP–NF contains official substance and preparation (product) monographs. It is available in English (printed and electronic formats), Spanish (print only), and Russian (printed only).

An official article is one that is recognized in *USP* or *NF*. An article is deemed to be recognized and included in a compendium when a monograph for the article

is published in the compendium and an official date is generally or specifically assigned to the monograph.

The title specified in a monograph is the official title for such article, for example, Aspirin Tablets. Other names considered to be synonyms of the official titles may not be used as substitutes for official titles.

Official articles include both official substances, for example, Aspirin (Salicylic Acid Acetate), and official products, for example, Aspirin Tablets. An official substance is a drug substance, excipient, dietary ingredient, other ingredient, or component of a finished device for which the monograph title includes no indication of the nature of the finished form.

An official product is a drug product, dietary supplement, compounded preparation, or finished device for which a monograph is provided.

All articles for which monographs are provided in *USP–NF* are legally marketed in the United States or are contained in legally marketed articles, as in the example of excipients [9]. There are few exceptions where the monograph was developed upon request from an international body, such as the World Health Organization (WHO), and the product is not marketed in the United States. Some examples are Zinc Sulfate Tablets and Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

A *USP–NF* monograph for an official substance or preparation may consist of various components, including the article's name; definition; packaging, storage, and other requirements; and a specification. The specification consists of a series of universal tests (description, identity/identification, impurities, and assay) and specific tests, one or more analytical procedures for each test, and acceptance criteria. Ingredients are defined as either drug substances or excipients. An excipient is any component, other than the active substance(s), intentionally added to the formulation of a dosage form. Excipients are not necessarily inert. Drug substances and excipients may be synthetic, semisynthetic, drawn from nature (natural source), or manufactured using recombinant technology. Drugs that consist of larger molecules and mixtures requiring a potency test are usually referred to as biologicals or biotechnological articles [9].

Several tests in *USP–NF* monographs for drug products have acceptance criteria that are calculated based on the product label claim. The information about the product label claim approved by the FDA for the products to be marketed in the United States is stated in the Orange Book available in the FDA's website (www.fda.gov/drugs). From the tests stated in a *USP–NF* monograph for drug product, the Assay and Dissolution/Drug release tests are the ones that, in most cases, are calculated considering the label claim. In the USP monograph for Nifedipine Extended-Release Tablets, the acceptance criteria for the Assay test is "… contain NLT 90.0% and NMT 110.0% of the labeled amount of nifedipine." The FDA approved nifedipine Extended-Release Tablets containing 30, 60, and 90 mg nifedipine per tablet.

General chapters provide frequently cited procedures, sometimes with acceptance criteria, with the intent to compile into one location repetitive information that appears in many monographs. Some examples of general chapters are <791> *pH*, <467> *Residual Solvents*, and <711> *Dissolution* [9]. General test chapters (those that are enforceable by the FDA) are numbered <1> to <999>, and general

information chapters (those serving only as guidelines) are numbered between <1000> and <1999>. General chapters specific to dietary supplements are included in numerical order with the rest of the general chapters in USP and are numbered above <2000>, for example, <2012> *Microbial Enumeration Tests—Nutritional and Dietary Supplements* [9].

In addition to the monographs and general chapters, *USP–NF* also contain information regarding reference standards, reference tables, and instructions for the preparation of reagents, indicators, and solutions that are referred to in monographs and general chapters. Reference Tables include information regarding appropriate containers for dispensing capsules and tablets as related to the container definitions in the *General Notices and Requirements*, description and solubility characteristics, atomic weights, alcoholometric values, intrinsic viscosity values, and thermometric equivalents (Fahrenheit to Celsius conversions) [12].

Flexible monographs. At times, an ingredient and/or a drug product, including dietary supplement ingredients and products and biologicals and biotechnological ingredients and products, exhibit different attributes that have been determined by the FDA not to affect their safety and/or efficacy, that is, their identity as official ingredients and products. Examples include different polymorphic forms, impurities, hydrates, and performance tests such as dissolution, drug release, and disintegration. In these instances, *USP–NF* will allow different tests, procedures, and/or acceptance criteria reflecting these different attributes within a single monograph, with suitable validation [13]. One of the first uses of the flexible monograph approach was for modified-release dosage forms approved by the FDA with different dissolution conditions [14,15] and then expanded for any dosage form approved by the regulatory agency with different dissolution conditions.

The approach for flexible monographs is very clear in the USP monograph for paclitaxel, an antineoplastic drug. The innovator of this product isolates paclitaxel from natural sources, the first generic manufacturer obtains the drug substance from a semisynthetic process, and the second generic manufacturer from a plant cell fermentation process. Each one of these processes have a specific related compounds profile; therefore, the USP monograph for paclitaxel has three different related compounds tests with different chromatographic conditions, different list of related compounds, and different acceptance criteria, specific for each one of the processes used to produce paclitaxel.

USP–NF Organization and Revision Process

USP–NF is printed as a three-volume set. Volume 1 includes front matter (Mission and Preface, People, Governance pages and websites, and Admissions/Annotations). It also includes *USP General Notices*, general chapters, dietary supplement general chapters, reagents, reference tables, dietary supplement monographs, *NF Admissions*, excipients, and *NF* monographs. Volumes 2 and 3 include USP monographs. To facilitate convenient use and reference, all three volumes include the full index as well as the *USP General Notices* and the *Guide to General Chapters*.

Excipient monographs usually are presented in *NF* but also may appear in *USP* with suitable cross-referencing when they are also drug substances. One example is the USP monograph for Benzalkonium Chloride, which can be used as a drug substance

because of its pharmacological action and/or as a preservative. The Excipients section (Volume 1) presents a tabulation of excipients by functional category [9].

Revisions to *USP–NF*

USP–NF is continuously revised. Revisions are presented annually as standard revisions in *USP–NF* and in twice yearly supplements and, as accelerated revisions, on USP's website (Errata, Interim Revision Announcements [IRAs], and Revision Bulletins).

Standard Revisions. USP's Standard Revision Process calls for publication of a proposed revision in the *Pharmacopeial Forum* for a 90-day notice and comment period and after the revision is approved by the relevant USP Expert Committee, publication in the next *USP–NF* or *Supplement*, as applicable.

Accelerated Revisions. The accelerated revision process is used to make revisions to *USP–NF* official more quickly than through USP's standard revision process. Accelerated revisions, which include Errata, IRAs, and Revision Bulletins, are posted on USP's website and do not always require notice and comment and allow for a revision to become official before the next *USP–NF* or *Supplement*.

Errata. An erratum (errata) is content erroneously published in a USP publication that does not accurately reflect the intended official or effective requirements as approved by the Council of Experts. These typically are changes that do not have a broad impact on the standards. Errata are not subject to public comment and become official when posted to the USP website. Errata are incorporated into the next available *USP–NF* or *Supplement*. The most frequent use of errata is to correct typographic errors in the text. One example would be an error in the units of the internal diameter of a high-performance liquid chromatography column, where 4.6 cm was published when it should have been 4.6 mm.

IRAs. An IRA appears in *Pharmacopeial Forum* first as a Proposed IRA with a 90-day comment period. If there are no significant comments in that period, the IRA becomes official in the New Official Text section of USP's website, with the official date indicated. IRAs are incorporated into the next available *USP–NF* or *Supplement*.

Revision Bulletins. If circumstances require rapid publication of official text, a revision or postponement may be published through a Revision Bulletin. Revision Bulletins are posted on USP's website with the official date indicated. Revision Bulletins are incorporated into the next available *USP–NF* or *Supplement* [9]. One of the most common uses of Revision Bulletins is for the inclusion of additional Dissolution and/or Disintegration or Drug release tests. One example is the case of Tamsulosin Hydrochloride Capsules. The FDA approved this product for the US market on April 1997 and its USP monograph became official in the Second Supplement of *USP 32* on December 2009. From March to July 2010, the FDA approved eight generic versions of Tamsulosin Hydrochloride Capsules, each one with a different dissolution test from the one stated in the USP monograph. All eight dissolution tests were included in the USP monograph through a Revision Bulletin official on October 2010.

For industry, the accelerated revisions carry the same compliance requirements as the *USP–NF* or its *Supplements*.

Pharmacopeial Forum

The *Pharmacopeial Forum* (http://www.usppf.com) is USP's official publication for public notice and comment. The *Pharmacopeial Forum* is available at no cost online. Proposals for revision are presented in the In-Process Revision or the Proposed IRA (see above) sections and represent draft revision that are expected to advance to official status pending final review and approval by the relevant Expert Committee. It includes proposed changes and additions to the *USP–NF*, including Stage 4 Harmonization, and Stimuli articles for which USP is seeking public comments. All proposals, including IRAs, will have a 90-day comment period.

Supplements

Supplements to *USP–NF* follow a standard schedule each year: The *First Supplement* is published in February and becomes official August 1. The *Second Supplement* is published in June and becomes official December 1. The *USP–NF* online version is updated with each *Supplement* or annual revision. The Index in each *Supplement* is cumulative and includes citations to the annual revision and, for the *Second Supplement*, citations to the *First Supplement*. The contents of the two *Supplements* are integrated into the annual edition of the following year, along with new official revisions that have been adopted since the *Second Supplement* to the previous compendia.

USP Reference Standards

When approved for use as a comparison standard as a component of a USP monograph or other compendial procedure, use of *USP–NF* reference standards promotes uniform quality of drugs and supports reliability and consistency by those performing compliance testing and the other users of *USP–NF*, including manufacturers, buyers, and regulatory authorities. USP reference standards are evaluated via careful characterization studies and collaborative testing followed by review and approval of the compendial use of the reference material by Expert Committees of the Council of Experts.

Commentary

In accordance with USP's Rules and Procedures of the Council of Experts, USP publishes all proposed revisions to the *USP–NF* for public review and comment in the *Pharmacopeial Forum*. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be published again in *Pharmacopeial Forum* for further notice and comment in accordance with the Rules and Procedures. In cases when proposals advance to official status without republication in *Pharmacopeial Forum*, a summary of comments received and the appropriate Expert Committee's responses are published in the Commentary section of the USP website at the time the revision is published. The Commentary is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of the Expert Committee's response to public comments.

Public Participation

Although USP's Council of Experts is the ultimate decision-making body for *USP–NF* standards, these standards are developed by an exceptional process of public involvement and substantial interaction between USP and its stakeholders, both domestically and internationally. Participation in the revision process results from the support of many individuals and groups and also from scientific, technical, and trade organizations.

Requests for Revision of the USP–NF, whether new monographs or general chapters or those needing updating, contain information submitted voluntarily by manufacturers and other interested parties. At times, USP staff and Expert Committees may develop information to support a Request for Revision. USP has prepared a document entitled *Guideline for Submitting Requests for Revision to USP–NF* (available at http://www.usp.org under Submission Guidelines). Via *Pharmacopeial Forum*, USP solicits and encourages public comment on these revision proposals. Comments received are considered by the Expert Committees, who determine whether changes should be made to the proposed revisions based on such comments. Proposed standards are finalized when Expert Committees vote to make them official text in *USP–NF*. Thus, the USP standards-setting process gives those who manufacture, regulate, and use therapeutic products the opportunity to comment on the development and revision of *USP–NF* standards. Figure 14.2 shows the public review and comment process and its relationship to standards development.

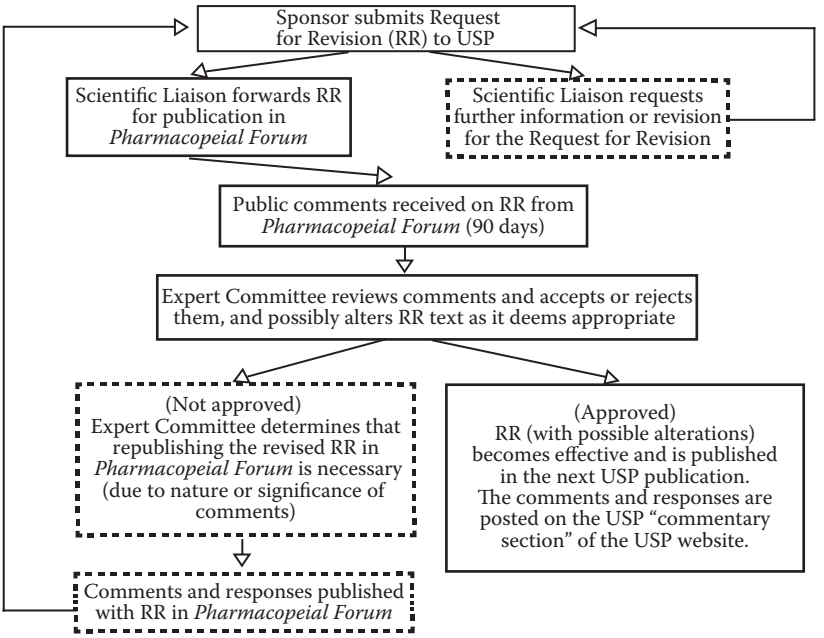
Sponsor submits Request for Revision (RR) to USP
Scientific Liaison forwards RR for publication in *Pharmacopeial Forum*
Scientific Liaison requests further information or revision for the Request for Revision
Public comments received on RR from *Pharmacopeial Forum* (90 days)
Expert Committee reviews comments and accepts or rejects them, and possibly alters RR text as it deems appropriate
(Not approved) Expert Committee determines that republishing the revised RR in *Pharmacopeial Forum* is necessary (due to nature or significance of comments)
(Approved) RR (with possible alterations) becomes effective and is published in the next USP publication. The comments and responses are posted on the USP "commentary section" of the USP website.
Comments and responses published with RR in *Pharmacopeial Forum*

FIGURE 14.2 USP's standards-setting public review and comment process.

Working with the FDA

As specified in US law, USP works with the Secretary of the Department of Health and Human Services in many ways. The principal agency in the Department for this work is the FDA. The FDA liaison program allows the FDA representatives to participate in Expert Committee and expert panel meetings, enabling interactions between the FDA scientific staff and Expert Committees. Staff in the FDA centers who are responsible for review of compendial activities provide specific links and opportunities for exchange of comments [9].

USP AND GENERIC PRODUCTS

Generic products in the United States are approved by the Office of Generic Drugs (OGD) in the FDA. To market a prescription or over-the-counter generic drug, an abbreviated new drug application (ANDA) must be submitted to the OGD. This office decides whether a certain generic product is therapeutically equivalent to its corresponding Reference Listed Drug (RLD). To be deemed therapeutically equivalent to the corresponding reference product, the generic must provide evidence that the generic is pharmaceutically equivalent to the corresponding RLD, adequately labeled, manufactured in compliance with current good manufacturing practice regulations, and bioequivalent to the RLD. A therapeutically equivalent generic product is interchangeable with the RLD [16].

Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet compendial or other applicable standards (i.e., strength, quality, purity, and identity). Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

The primary difference between the requirements of a “full” and an “abbreviated” application is that the preclinical and clinical data in the NDA that establishes the safety and efficacy of the drug product do not need to be repeated for the ANDA. The generic drug product is of comparable purity and quality to the RLD.

When the FDA receives an ANDA, a monograph defining certain key attributes of the drug substance and drug product is frequently available in the USP. Sometimes, literature information on drug product attributes (i.e., impurities profile, solubility, and in vitro dissolution) may also be available. These public standards and literature data play a significant role in the regulatory assessment process of an ANDA.

The safety and quality of the drug substance and drug product in a generic product can be impacted by the presence of impurities and degradation products. In establishing impurity or degradation products acceptance criteria, the first critical consideration is whether an impurity or degradation product is specified in the USP. If there is a monograph in the USP that includes a limit for an identified specified impurity or degradation product, it is recommended that the acceptance criterion be set no higher than the official compendial limit. However, if the level of the impurity or degradation product is above the level specified in the USP, qualification would

be recommended. Then, if appropriate qualification has been achieved, the company may wish to petition the USP for revision of the impurity's or degradation product's acceptance criterion. Where there are specified impurities or degradation products identified by the USP monograph (e.g., Related Compound 1), the proposed limits may be based solely upon the USP limits without further analysis of the RLD. However, an important point to stress in this regard is that if there are some specified impurities or degradation products (e.g., Related Compound 2) not explicitly identified by the USP monograph, their limits must be justified by some other means. Despite the existence of USP compendial analytical methods for monitoring impurities and degradation products, the suitability of the compendial method to the generic product should be demonstrated [17].

If there is a USP monograph for the drug product containing dissolution, disintegration, or drug release tests, it is recommended that the appropriate USP method be submitted in the ANDA. If there is no USP method available, the recommendation is to use the dissolution method proposed in the FDA-recommended dissolution methods database (available at www.fda.gov/drugs). If the USP and/or the FDA methods are not available, a new dissolution method needs to be developed and validated. In the case of modified-release dosage forms, in addition of using the USP or FDA methods, it is recommended to generate the release profiles using at least three other dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer) and water [18].

PHARMACOPEIAS WORLDWIDE

Pharmacopeias are published in many other nations, and USP has formed working relationships with sponsoring regulatory bodies around the world. USP is one of the only private nongovernmental pharmacopeias, and this nongovernmental status allows it to work for public health across geographic and political borders. An index of the national pharmacopeias is maintained by the WHO [19].

PHARMACOPEIAL HARMONIZATION

The Pharmacopeial Discussion Group (PDG), comprising representatives from the European Directorate for the Quality of Medicines (which publishes the *European Pharmacopoeia*), the Japanese Pharmacopoeia, and USP, was formed in 1989 (WHO serves as an observer). It preceded the formation of the International Conference on Harmonization, made up of national regulatory officials and pharmaceutical manufacturers, and USP has participated actively in its harmonization efforts. The PDG meets periodically to work on harmonization of excipient monographs and general chapters. The objective is the reduction of manufacturers' burdens in performing testing by differing procedures or by using differing acceptance criteria. An effort is made to maintain an optimal level of science consistent with the protection of public health. The PDG defines harmonization of a pharmacopeial general chapter or other document as being when a pharmaceutical substance or product is tested by the harmonized procedure given by the document the same analytical result and the same accept/reject decision is reached. Full harmonization may not always be possible.

In such cases, the PDG attempts what is termed harmonization by attribute where some elements of a monograph or general chapter may be harmonized, whereas others may not. Harmonization by attribute requires consultation of the content of the individual pharmacopeia for the nonharmonized elements.

In recent years, USP has started to engage not only in "retrospective harmonization" but also in "prospective harmonization" so that conflicts in standards could be addressed and harmonized before they became official in different countries. In addition, since 1996, USP has participated in the Pan American Health Organization–sponsored Pan American Network for Drug Regulatory Harmonization at the level of the Steering Committee and in the Working Groups, particularly the Pharmacopeial Working Group.

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15 Legal and Legislative Hurdles to Generic Drug Development, Approval, and Marketing

Arthur Y. Tsien

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INTRODUCTION

The preceding chapters have discussed a variety of scientific, technical, and regulatory considerations related to the development and approval of generic drug products. To compliment that discussion, this chapter is written from the perspective of a lawyer specializing in the drug regulatory process. This chapter discusses a variety of legal and legislative considerations as well as some miscellaneous regulatory considerations. There are, of course, no clear lines dividing the "scientific," "regulatory," and "legal" arenas in the context of generic drug development and approval. Although some of the disputes discussed in this chapter have a "scientific" underpinning, the matters have often presented themselves in the litigation context.

There have been a number of important amendments to the Federal Food, Drug, and Cosmetic Act (FDC Act) in recent years that affect generic drugs. These include the following:

- Food and Drug Administration Modernization Act (FDAMA), enacted in November 1997*
- Best Pharmaceuticals for Children Act (BPCA), enacted in January 2002†
- Pediatric Research Equity Act (PREA), enacted in December 2003‡
- Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA)§
- Food and Drug Administration Amendments Act of 2007 (FDAAA)¶

* Pub. L. No. 105-115.
† Pub. L. No. 107-109.
‡ Pub. L. No. 108-155.
§ Pub. L. No. 108-173.
¶ Pub. L. No. 110-85.

- QI Program Supplemental Funding Act of 2008 (QI Act)*
- Biologics Price Competition and Innovation Act of 2009 (BPCIA)†

As of this writing, the FDA's interpretations of some of these provisions are in a state of flux. Thus, a prudent prospective abbreviated new drug application (ANDA) or 505(b)(2) NDA sponsor that does not have the requisite in-house resources would be well advised to consult with competent regulatory consultants or legal counsel on these issues during the business decision-making, drug development, and drug approval processes.

Over the years, legislation has been introduced, but not enacted into law, to address many scenarios discussed in this chapter. Several situations where legislation is highly likely to be enacted or where there appears to be widespread recognition that legislation is needed have been noted in this chapter. However, specific pending legislation has not been cited.

Some of the examples described in this chapter do not involve solid oral dosage forms. These examples have nevertheless been included because similar situations could arise in the context of an ANDA or a 505(b)(2) NDA for a solid oral dosage form.

CITIZEN PETITIONS AND LEGAL CHALLENGES TO GENERIC DRUG APPROVALS

A citizen petition is nothing more than the formal procedural mechanism for any individual or entity to ask the FDA to take, or refrain from taking, some specified agency action. The requirements for citizen petitions are set forth in FDA regulations.‡

Not surprisingly, innovator drug sponsors have mounted a number of challenges to FDA approval decisions, or anticipated approval decisions, for generic versions of their drug products. Frequently, innovator firms have filed citizen petitions with the FDA, raising reasons why the FDA should not grant an anticipated approval of a generic version of their products. Citizen petitions can also be filed by generic firms for a wide variety of purposes. For example, they include ANDA suitability petitions and petitions addressing 180-day exclusivity disputes.

The submission of a citizen petition to the FDA by an innovator or generic firm seeking to affect the approval of generic products serves several purposes. First, it is possible that the FDA may grant the requested relief. (The FDA has not done so on most occasions.) Second, even if the FDA does not grant the requested relief, its consideration of a citizen petition can be a lengthy process that may delay the approval of the generic product. Third, and perhaps most importantly, the submission of a citizen petition helps counter the argument frequently made by the FDA (and other government agencies) that a person challenging an agency action in court has not first "exhausted" all available administrative remedies. The reason that courts may apply the "exhaustion" requirement is to help conserve judicial resources, by ensuring that

* Pub. L. No. 110-379.
† Pub. L. No. 111-148.
‡ 21 CFR § 10.30.

courts are not asked to address situations that might have been resolved had relief been sought from the administrative agency in the first instance.

On a number of occasions, adversely affected innovator drug sponsors have sought judicial review of the FDA's ANDA approval decisions. In some cases, the FDA has denied a relevant citizen petition contemporaneously with an ANDA approval; in other cases, the FDA did not act on the petition despite the granting of the challenged ANDA approval, and the innovator firm regarded the FDA's ANDA approval as tantamount to denial of its petition. Generally, the innovator firm has sued the FDA, seeking to block approval of the generic product. Typically, the generic firm or firms involved have been allowed to intervene in the lawsuit to protect their economic interests in their ANDA approvals.

In a number of situations involving disputes over 180-day generic drug exclusivity, an adversely affected ANDA sponsor has sued the FDA regarding a 180-day exclusivity decision. As with challenges brought by innovator drug sponsors, those challenges are often preceded by the submission of a citizen petition to the FDA. In these disputes, it has been commonplace for other affected ANDA sponsors—and sometimes the sponsor of the innovator product—to be allowed to intervene in the lawsuit to protect their rights.*

A provision added to the FDC Act in 2007 addresses citizen petitions and other efforts to block or delay the approval of an ANDA or a 505(b)(2) NDA.† The provision is intended to address widely held concerns of the generic drug industry and others that citizen petitions are sometimes used solely or primarily for the purpose of prolonging the innovator firm's monopoly. Citizen petitions that relate solely to the timing of ANDA final approval as a result of 180-day exclusivity are excluded from the new provision. Similarly, a petition submitted by the sponsor of an application that relates solely to that sponsor's application is outside the scope of the new provision.

The FDA is prohibited from delaying the approval of a pending ANDA or 505(b)(2) NDA unless the request is in the form of a citizen petition, and the FDA determines that "a delay is necessary to protect the public health." If the FDA determines that a delay is necessary, the FDA must so notify the sponsor of the pending application within 30 days after making its determination that a delay is necessary. The notification must include a brief summary of the specific substantive issues raised.

The FDA is required to make a final decision on a petition related to an ANDA or 505(b)(2) NDA final approval within 180 days, which time period cannot be extended for any reason. If the FDA fails to issue a timely final decision, the FDA's failure to act is deemed to be final agency action for judicial review purposes. (This does not mean that a court will automatically consider a challenge to a petition. For example, a court could refuse to consider a lawsuit on the basis that the matter is not considered "ripe" for judicial determination.‡) If a lawsuit is filed against the FDA with regard to any issue raised in a petition before the FDA has issued a final decision or 180 days have passed without FDA action, the court is required to dismiss the lawsuit without prejudice on the basis that administrative remedies were not exhausted.

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* *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998) (involving glyburide) (allowing innovator firm to intervene).

† 21 USC § 355(q) (added by FDAAA).

‡ *Pfizer, Inc. v. Shalala*, 182 F.3d 975 (D.C. Cir. 1999) (involving nifedipine).

Citizen petitions within the scope of the provision and comments on such petitions are required to contain a detailed certification or verification, under penalty of perjury. The certification or verification must disclose the date on which information regarding the action requested first became known to the party on whose behalf the petition or comment is submitted. In addition, the petition or comment must disclose the identity of any persons or organizations from whom the submitter of the petition or comment has received, or expects to receive, compensation. Thus, "blind" petitions and comments submitted by law firms, consultants, and experts are no longer possible if such petitions or comments relate to blocking the final approval of an ANDA or 505(b)(2) NDA.

If the final approval of an ANDA that has 180-day exclusivity rights is delayed because of a petition, the 30-month period for obtaining tentative approval to avoid forfeiture of the 180-day exclusivity rights (discussed in MMA Rules) is extended by the period during which the petition was pending before the FDA.

The FDA has interpreted this new provision as applying only to citizen petitions submitted to the agency on or after September 27, 2007.* The FDA has generally adhered to the 180-day decision timeframe for "new" petitions. However, "old" petitions (submitted to the FDA before September 27, 2007) continue to languish, sometimes for many years.

On a related note, in response to widespread criticism, the FDA has begun to "decouple," when appropriate, drug approval decisions from decisions to deny citizen petitions that seek to block or delay those drug approvals.†

EXCLUSIVITY ISSUES

Five-Year New Chemical Entity Exclusivity

The Hatch–Waxman Amendments grant the sponsor of an NDA for a drug product containing what is commonly referred to as a "new chemical entity" or "NCE," that is, an active ingredient that was not previously used in an approved drug product, a 5-year period, which starts running with the date of NDA approval, during which the FDA cannot accept any ANDAs or 505(b)(2) NDAs based on the innovator product for review.‡ However, if the ANDA or 505(b)(2) NDA sponsor challenges an "Orange Book" patent on the innovator product by submitting a Paragraph IV certification (which contends that the patent is invalid or not infringed), the ANDA or 505(b)(2) NDA may be submitted 4 years after the date of initial NDA approval (often referred to as the "NCE minus 1" or "NCE-1" date), thereby potentially saving the ANDA or 505(b)(2) NDA sponsor 1 year.

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* *Guidance for Industry: Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*, June 2011. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf. Accessed June 13, 2013.

† FDA July 28, 2008 letter to Ernest Lengle, Docket No. FDA-2008-P-0069. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0069-0010. Accessed June 13, 2013 (involving irinotecan); ANDAs in question approved in February 2008.

‡ 21 USC § 355(j)(5)(F)(ii) and (c)(3)(E)(ii).

As noted, NCE exclusivity bars the submission of an ANDA or 505(b)(2) NDA to the FDA. In this regard, it operates differently from other exclusivity provisions, which bar FDA final approval. Thus, at least in theory, a Paragraph IV ANDA or 505(b)(2) NDA submitted on (or soon after) the NCE-1 date could, in the absence of patent litigation and the resulting delay in final approval (discussed in 30-Month Delay of ANDA and 505(b)(2) NDA Final Approval below), receive final approval before the 5-year NCE exclusivity has expired.

Hatch–Waxman exclusivity operates independently of any patents that protect the active ingredients or other aspects of the innovator product. In most (but not all) cases, the innovator product is protected by one or more "blocking" patents (typically on the active ingredient itself, the use of the active ingredient, or both) until well after the expiration of the 5-year NCE exclusivity. Because challenges to these "blocking" patents usually do not succeed, 5-year exclusivity is generally not a determinative factor in when generic competition will begin.

Eligibility for NCE exclusivity is determined by examining the "active moiety" of a drug product. The "active moiety" excludes appended portions of the molecule that caused the substance to be an ester, salt, or other noncovalent derivative.* The FDA's interpretation that a prodrug that is not an ester, salt, or other noncovalent derivative may be eligible for NCE exclusivity was upheld on judicial review.†

A drug product containing a combination of a previously approved active moiety and a new active moiety is not eligible for NCE exclusivity.‡

The FDA's current interpretation is that a single enantiomer of a previously approved racemate is not an NCE.§ In 1997, the FDA sought public comment on whether a single enantiomer of a previously approved racemate should be viewed as an NCE.¶ However, the FDA did not follow up with any pronouncements regarding affirmation of, or change to, its interpretation.

In 2007, the FDC Act was amended to provide for a very limited optional exclusivity period for certain drugs containing single enantiomers, under which the sponsor of a "full" 505(b)(1) NDA can elect for the enantiomer to be considered a new active moiety that is eligible for 5-year NCE exclusivity if a number of conditions are met.** The conditions include the application does not rely on any studies that support the approval of the racemic drug, and the enantiomer is not intended for a use that is in a "therapeutic category" for which the racemic drug or any other enantiomer of the racemic drug has been approved. The election may only be made in a NDA submitted before October 1, 2012. As of the time of this writing, a legislative extension of that deadline seems likely.

Three-Year Exclusivity for Product "Improvements"

The Hatch–Waxman Amendments also provide NDA sponsors with a 3-year period free from generic competition for the approval of an NDA or supplemental NDA

* 21 CFR § 314.108(a) (definitions of "new chemical entity" and "active moiety").
† *Actavis Elizabeth LLC v. United States Food and Drug Administration*, 625 F.3d 760 (D.C. Cir. 2010).
‡ 21 CFR § 314.108(a) (definitions of "new chemical entity" and "active moiety").
§ 54 Fed. Reg. 28,871, 28,898 (July 10, 1989) and 59 Fed. Reg. 50,338, 50,359 (October 3, 1994).
¶ 62 Fed. Reg. 2167 (Jan. 15, 1997).
** 21 USC § 355(u) (added by FDAAA).

for a drug product containing a previously approved active ingredient, when the approval is supported by new clinical studies (other than bioavailability studies) "essential" to the approval.* Unlike 5-year NCE exclusivity, 3-year exclusivity does not bar the submission of ANDAs or 505(b)(2) NDAs to the FDA; it only prohibits final approval of an ANDA or 505(b)(2) NDA.

A challenge to the FDA's decision that a particular clinical trial is, or is not, "essential" to an approval is unlikely to succeed. One court rejected such a challenge, noting that the FDA's evaluation of clinical trials and related determinations are within its area of expertise and that the courts must grant wide deference to these determinations.†

When the FDA grants 3-year exclusivity for the approval of a new drug product or new form of an approved drug product containing a previously approved active ingredient, generic competition is effectively blocked for 3 years with little recourse to an ANDA or 505(b)(2) NDA sponsor. A situation that is of far greater practical significance to the generic industry is 3-year exclusivity granted for the approval of a supplemental NDA that provides for revised labeling. In general, the FDA has interpreted 3-year exclusivity narrowly in this situation. In the case of FDA approval of a new (additional) indication, the FDA allows the generic sponsor to seek ANDA or 505(b)(2) NDA approval based on the "old" labeling, "carving out" or deleting the newly approved, additional indication.‡ This practice has been upheld in two judicial challenges, one of which involved the FDA's approval of a generic product for an unprotected indication, where the innovator drug product had a separate indication protected by orphan drug exclusivity.§

The situation becomes more problematic where the NDA sponsor obtains 3-year exclusivity for revised labeling that provides replaces or augments certain aspects of the previously approved labeling. For example, a titration-dosing requirement may be eliminated, the duration of an infusion schedule may be changed, or information regarding the safe and effective use of the drug product in combination with a different drug product may be added to the approved labeling. In a number of administrative decisions responding to citizen petitions regarding labeling "carve outs," the FDA has stated its intention to address these situations on a case-by-case basis. The FDA will approve a generic product with carved out labeling if the Agency finds that the "old" labeling was not withdrawn for safety or effectiveness reasons, and omission of exclusivity- or patent-protected labeling does not render the proposed generic product with carved out labeling less safe or less effective than the reference drug for all remaining, nonprotected conditions of use.¶ Using this rationale, the FDA has approved close to 20 generic products with labeling carve outs while rejecting only two such approvals.**

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* 21 USC § 355(j)(5)(F)(iii) and (iv) and (c)(3)(E)(iii) and (iv).

† *Upjohn Co. v. Kessler*, 938 F. Supp. 439 (W.D. Mich. 1996) (upholding FDA's decision not to grant 3-year exclusivity for OTC minoxidil).

‡ 21 CFR § 314.94(a)(8)(iv).

§ *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002) (involving levocarnitine); *Bristol-Myers Squibb Company v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) (involving captopril).

¶ 21 CFR § 314.127(a)(7).

** See, e.g., February 24, 2011 letter to Robert Traynor, Docket No. FDA-2010-P-0545 at 9, n.14 and decisions cited. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0545-0006. Accessed June 13, 2013 (involving levoceterizine).

Seven-Year Orphan Drug Exclusivity

Orphan drug exclusivity bars the FDA from issuing final approval to an ANDA based on the orphan product for 7 years.* It also bars the FDA final approval of a 505(b)(2) NDA for the same or a similar drug, unless the subsequent drug can be shown to be clinically superior to the drug entitled to exclusivity.†

Orphan drug exclusivity does not prevent the FDA from approving an ANDA for an indication no longer protected by orphan exclusivity, where another indication still entitled to orphan exclusivity was "carved out" from the generic product's labeling.‡

180-Day Generic Drug Exclusivity

The Hatch–Waxman Amendments provide for a 180-day period of exclusivity, where the first Paragraph IV ANDA sponsor (which challenges an Orange Book patent on the innovator product being copied) is entitled to a 180-day period during which it is the only generic product on the marketplace.§ This provision has been the source of much litigation in recent years, with some unresolved issues.

In 2003, the MMA amended the FDC Act and made very substantial revisions regarding 180-day exclusivity. With minor exceptions, these changes are prospective in nature, applying only to situations where the first Paragraph IV ANDA based on a reference product was submitted to the FDA after December 8, 2003. Thus, as of the time of this writing, there are a dwindling number of ANDAs governed by the "old" 180-day exclusivity rules. "Old" ANDAs and "new" ANDAs (governed by the MMA rules) are discussed separately below.

General Considerations

As currently interpreted by the courts and the FDA, 180-day exclusivity is available to the sponsor of the first substantially complete Paragraph IV ANDA, regardless of whether it prevails in patent litigation¶ or is even sued for patent infringement at all.** This exclusivity has become an important business consideration for ANDA sponsors. Without doubt, 180-day exclusivity is highly valuable, as the first firm to enter the generic marketplace can often "fill the pipeline" and derive a long-term benefit from its 180-day head start. Unfortunately, business planning in this important area is stifled by the FDA's typical refusal to disclose whether a firm is entitled to 180-day exclusivity before its ANDA is ready for final approval. The FDA's website†† only discloses whether a Paragraph IV ANDA has been submitted in connection with a particular innovator drug product and the date of the first ANDA (for submissions

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* 21 USC § 360cc(a).

† 21 CFR § 316.3(b)(13) (definition of "same drug" for orphan exclusivity purposes).

‡ *Sigma-Tau Pharmaceuticals, supra*, n. §, p. 339.

§ 21 USC § 355(j)(5)(B)(iv).

¶ *Mova, supra*, n. *, p. 336.

** *Purepac Pharmaceutical Co. v. Friedman*, 162 F.3d 1201 (D.C. Cir. 1998) (involving ticlopidine).

†† http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM261594.pdf. Accessed June 13, 2013.

made on or after March 2, 2004); no additional details are provided. In some cases, ANDA sponsors can draw reasonable inferences about their actual entitlement to 180-day exclusivity from publicly available information in patent infringement litigation or even from publicly available information about ANDA reference numbers of tentatively approved ANDAs. However, this information is not always available (e.g., some or all of Paragraph IV ANDA applicants may not be sued) and may not be reliable in all regards.

In general, entitlement to 180-day exclusivity is determined by the date on which the FDA actually receives the first substantially complete Paragraph IV ANDA. If the ANDA sponsor fails to give notice of its Paragraph IV certification in timely fashion, the "penalty" is that sponsor's "priority date" is delayed until the date on which notice is actually sent. This interpretation has been upheld as reasonable.*

The FDA recognizes that 180-day exclusivity is a valuable right that can be sold or traded. This recognition provides a valuable opportunity for an ANDA sponsor entitled to 180-day exclusivity that is, for whatever reason, not positioned to receive meaningful benefit from its exclusivity. (For example, that sponsor may be unable to obtain final ANDA approval.) The FDA permits exclusivity to be "selectively waived" in favor of one or more specific ANDA sponsors otherwise eligible for final approval only if the exclusivity has been "triggered" and is then running. If the exclusivity has not been "triggered," the FDA only permits it to be "relinquished" in its entirety, permitting all otherwise eligible ANDA sponsors to receive final approval.† In a particular situation, there may be no meaningful difference between a "selective waiver" and a complete "relinquishment" of 180-day exclusivity.

For 180-day exclusivity purposes, each strength or form of an innovator drug product is treated separately. Thus, a court decision of patent invalidity or noninfringement involving one strength or form has no effect on 180-day exclusivity for a different strength or form.‡ The FDA's longstanding view that 180-day exclusivity does not survive patent expiration has been upheld.§

The 180-day exclusivity only affects ANDAs. 505(b)(2) NDAs are not eligible for, and are not affected by, 180-day exclusivity.

Pre-MMA Rules

An ANDA sponsor's 180-day exclusivity is "triggered," or starts running, with the earlier of two events: the date that ANDA sponsor begins commercial marketing or the date of a "court decision" finding the patent in question invalid or not infringed.¶ As interpreted by the courts and the FDA, the court decision of invalidity or noninfringement can involve that patent and any ANDA sponsor; it need not involve

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* *Purepac Pharmaceutical Co. v. Thompson*, 354 F.3d 877, 888-89 (D.C. Cir. 2004) (involving gabapentin).

† 64 Fed. Reg. 42,873, 42,881 (August 6, 1999) (proposed rule, subsequently withdrawn for unrelated reasons); *Boehringer Ingelheim Corporation v. Shalala*, 993 F. Supp. 1 (D.D.C. 1997) (involving ranitidine; upholding "selective waiver").

‡ *Apotex, Inc. v. Shalala*, 53 F. Supp. 2d 454 (D.D.C. 1999), summary affirmance, 1999 WL 956686 (D.C. Cir. 1999) (involving ranitidine; upholding FDA interpretation).

§ *Mylan Laboratories, Inc. v. Leavitt*, 484 F. Supp. 2d 109, 122 (D.D.C. 2007) (involving amlodipine).

¶ Former 21 USC § 355(j)(5)(B)(iv) (amended by MMA).

the ANDA sponsor entitled to exclusivity.* The MMA provided that, for all "old" ANDAs for which the 180-day exclusivity period had not yet been triggered, a US Court of Appeals for the Federal Circuit (Federal Circuit) decision of invalidity or noninfringement would serve as the trigger; a district court decision of invalidity or noninfringement would trigger the 180-day exclusivity period only if the time for appeal had lapsed and no appeal was taken.†

In some situations, the entire generic market can be blocked because of the existence of 180-day exclusivity. This situation can occur if no Paragraph IV ANDA applicant is sued for patent infringement (so the "court decision trigger" is never activated), and the first Paragraph IV ANDA applicant (entitled to 180-day exclusivity) is not able to begin commercial marketing (because it is unable to obtain final approval or, for example, supply problems keep it from beginning manufacture even if it has received final approval). It can also happen if the first Paragraph IV ANDA sponsor settles patent litigation in exchange for a patent license that starts on a future date. One possibility is for a subsequent Paragraph IV ANDA applicant to file a declaratory judgment lawsuit against the patent holder, seeking a declaration that the patent is invalid or not infringed. If obtained, such a declaratory judgment will serve as the "court decision trigger" that starts the running of the 180-day exclusivity period.‡ Difficulties with bringing a successful declaratory judgment lawsuit are discussed in Declaratory Judgement Actions. In addition, from a business perspective, the filing of a declaratory judgment lawsuit is undercut by the fact that a favorable decision benefits all generic sponsors, not just the company that bears the burden and cost of initiating the lawsuit.

The FDA states that it is regulating "directly from the statute" in the area of 180-day exclusivity,§ an approach that has been judicially sanctioned.¶ The FDA has adopted a "patent-by-patent" approach, under which a separate 180-day exclusivity period is potentially available in connection with each Orange Book patent. The FDA first addressed this issue in a situation where two ANDA sponsors were each the first to file a Paragraph IV certification on a different Orange Book patent. One patent expired before the 180-day period associated with that patent had been triggered. The FDA concluded that that patent and its associated 180-day exclusivity period were of no continuing relevance and did not prevent a 180-day exclusivity period in favor of the first Paragraph IV applicant on the later expiring Orange Book patent.**

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* *Granutec Inc. v. Shalala*, 1998 WL 153410 (4th Cir. April 3, 1998), 139 F. 3d 889 (4th Cir. 1998) (table) (involving ranitidine).

† MMA, § 1102(b)(3).

‡ The D.C. Circuit held that the dismissal of a declaratory judgment lawsuit for lack of subject matter jurisdiction does not serve as the "court decision trigger." *Teva Pharmaceuticals USA, Inc. v. Food and Drug Administration*, 441 F.3d 1 (D.C. Cir. 2006) (involving pravastatin). Although this decision arose under pre-MMA law, it is the author's view that it applies with equal force to situations governed by current (MMA) law, specifically, to forfeiture condition (I), discussed in MMA Rules.

§ E.g., 67 Fed. Reg. 66,593 (November 1, 2002).

¶ *Teva Pharmaceuticals, USA, Inc. v. U.S. Food and Drug Administration*, 182 F.3d 1003, 1005 (D.C. Cir. 1999) (involving ticlopidine).

** FDA August 2, 1999 letter to Robert Green, et al. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0188-0007. Accessed June 13, 2013 (involving cisplatin).

The FDA has also invoked the concept of "shared exclusivity."* Two ANDA sponsors, each of whom was the first to file a Paragraph IV certification to a different Orange Book patent, are allowed to share a single 180-day exclusivity period. The exclusivity period begins running with the earlier of onset of commercial marketing by either of the two firms sharing exclusivity or a court decision involving either Orange Book patent. Absent this pragmatic solution, the two firms would have had overlapping and conflicting 180-day exclusivity periods.

"Delisted" Orange Book patents have presented issues. According to a decision by the U.S. Court of Appeals for the District of Columbia Circuit (D.C. Circuit), the first ANDA sponsor to submit a Paragraph IV certification to a then-validly listed Orange Book patent is entitled to 180-day exclusivity, regardless of whether it was sued for patent infringement.† In determining whether a patent has been delisted at the time an ANDA with a Paragraph IV certification is submitted, the D.C. Circuit has upheld FDA's interpretation that the date that the FDA receives the NDA sponsor's delisting request is controlling, even if the patent is not actually removed from the print or electronic Orange Book until a later date.‡

By statute, any portion of the 180-day exclusivity period lost due to "overlap" with 6-month pediatric exclusivity (discussed in Six-Month Pediatrics Labeling Exclusivity) will be restored.§ This confusing statutory provision has been interpreted by the FDA to apply only to situations governed by pre-MMA law, where the "court decision trigger" starts the running of the 180-day exclusivity period.¶

MMA Rules

The MMA made several fundamental changes to 180-day exclusivity, which are, except as otherwise noted, only applicable prospectively to situations where no Paragraph IV ANDA for a reference product was submitted to the FDA before December 8, 2003.**

First, the MMA rejected FDA's patent-by-patent approach. Instead, only the first Paragraph IV ANDA sponsor or sponsors on the first day of submission of a Paragraph IV ANDA—defined as "first applicants"—are eligible to share in a single 180-day exclusivity period.††

Second, the court decision trigger was eliminated. The 180-day exclusivity period starts with commercial marketing by any first applicant; the marketing of an authorized generic (discussed in "Authorized Generics") by a first applicant also starts the 180-day exclusivity period.‡‡

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* See, e.g., FDA July 30, 2003 letter to Apotex Corporation. Available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm120608.htm. Accessed June 13, 2013 (involving paroxetine).

† *Ranbaxy Laboratories Limited v. Leavitt*, 469 F. 3d 120 (D.C. Cir. 2006) (involving simvastatin).

‡ *Teva Pharmaceuticals USA, Inc. v. FDA*, 548 F. 3d 103 (D.C. Cir. 2008) (involving risperidone). Although this case arose under pre-MMA law, it appears to the author that the court's conclusion is equally applicable to situations governed by current (MMA) law.

§ 21 USC § 355a(o) (added by BPCA, recodified by FDAAA).

¶ *Hi-Tech Pharmacal Co., Inc. v. U.S. Food and Drug Administration*, 587 F. Supp. 2d 13, 20 (D.D.C. 2008) (involving dorzolamide/timolol).

** MMA, § 1102(b)(1).

†† 21 USC § 355(j)(5)(B)(iv) (as amended by MMA).

‡‡ 21 USC § 355(j)(5)(B)(iv)(I) (as amended by MMA).

Third and finally, the MMA amended the FDC Act to provide for a detailed set of six independent "forfeiture events."* If a forfeiture event occurs with regard to a first applicant, that applicant forfeits its rights to 180-day exclusivity. If all first applicants forfeit, then no ANDA sponsor is eligible for 180-day exclusivity.

Although several of these forfeiture conditions are arguably internally inconsistent and capable of varying interpretations, the FDA has chosen not to address the interpretation of the forfeiture provisions through rulemaking or even through guidance documents. Rather, the FDA has sought limited public comment, generally by means of "Dear ANDA Applicant" letters and the posting of information on the FDA's website, before making decisions, which then may serve as "precedent" for future decisions.

Forfeiture condition (I), "failure to market," is the most complex of the six forfeiture conditions. It includes an interrelated set of "later of" and "earlier of" dates related to the dates of ANDA submission, final approval, final court decisions or court-approved settlement agreements that include a finding of patent invalidity or noninfringement, and patent delisting. The FDA interpreted the statutory provisions so that one or more Orange Book patents that serve as the basis for 180-day exclusivity for which there is no court decision of invalidity or noninfringement would effectively prevent the forfeiture condition from being operative.† Thus, as with pre-MMA ANDAs, the patentee's failure to sue any Paragraph IV ANDA sponsor on one or more Orange Book patents or a first applicant's settlement of patent infringement litigation that does not include an express finding of patent validity and infringement still allows the entire generic market to be blocked in many instances.

One of the dates in forfeiture condition (I) relates to patent delisting. That provision applies only if a patent is delisted pursuant to a patent delisting counterclaim in Paragraph IV patent litigation (discussed in Scope of Hatch–Waxman Patent Listing Provisions below); it does not apply to patents that are delisted voluntarily or following a judicial decision of patent invalidity.‡ Another date in forfeiture condition (I) relates to patent expiration. Premature patent expiration due to the patentee's failure to pay maintenance fees is not taken into consideration for 180-day exclusivity purposes.§

Forfeiture condition (IV) provides for forfeiture if the first applicant fails to receive "tentative approval" of its ANDA within 30 months, unless FDA requirements change. The FDA has interpreted this provision so that an ANDA sponsor entitled to 180-day exclusivity forfeits that exclusivity if it has not received final approval within 30 months, in a situation where that sponsor could not have received tentative approval because final approval was not blocked by any exclusivity periods or Paragraph III patent certifications.¶ In addressing citizen petitions that seek to

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* 21 USC § 355(j)(5)(D) (as amended by MMA).

† FDA January 17, 2008 letter to Marc Goshko, Docket No. FDA-2007-N-0269. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2007-N-0269-0003. Accessed June 13, 2013 (involving granisetron).

‡ *Teva Pharmaceuticals USA, Inc. v. Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010) (involving losartan).

§ *Apotex, Inc. v. Sebelius*, 700 F. Supp. 2d 138 (D.D.C.), affirmed per curiam, 384 Fed. Appx. 4 (D.C. Cir. 2010).

¶ FDA May 7, 2008 letter to William Rakoczy, et al., Docket No. FDA-2007-P-0249, at 10, n.17. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2007-N-0445-0026. Accessed June 13, 2013 (involving acarbose).

block or delay ANDA approvals, the FDAAA expressly provided that the number of days of delay attributed to such a petition is to be excluded from this 30-month period as well as from the 30-month period in "failure to market" forfeiture condition (I).*

Due to FDA delays in reviewing and approving ANDAs, the failure to obtain tentative approval within 30 months can lead to the forfeiture of 180-day exclusivity by the first applicant or applicants through no fault of their own. According to the FDA, "fault" is not taken into account in determining forfeiture under forfeiture condition (IV).†

In situations where there are multiple first applicants (such as situations involving the submission of multiple Paragraph IV ANDAs on the NCE-1 date), the failure to obtain tentative approval within 30 months has no practical effect unless all first applicants forfeit their 180-day exclusivity rights under forfeiture condition (IV).‡

Forfeiture condition (V) provides for forfeiture of 180-day exclusivity if there is a final decision of the Federal Trade Commission (FTC) or a final court decision that the ANDA sponsor had entered into an agreement with another ANDA sponsor, the NDA sponsor, or the patent owner in violation of antitrust laws. This forfeiture condition, unlike the others, applies to all pending ANDAs, without regard to when the first Paragraph IV ANDA was filed.§ The forfeiture condition has not been utilized to date. Based on the plain statutory language, the FDA rejected a request that the agency use this forfeiture condition to effect a forfeiture in a situation where the ANDA sponsor entitled to 180-day exclusivity had settled its Paragraph IV patent litigation, but there was no FTC or court decision regarding an antitrust violation.¶

Other forfeiture conditions are (II) the first applicant's ANDA is withdrawn or deemed withdrawn,** (III) the first applicant's Paragraph IV certifications to all relevant patents are withdrawn or amended,†† and (VI) all patents to which the first applicant had submitted Paragraph IV certifications expire.‡‡

Six-Month Pediatric Labeling Exclusivity

An innovator drug sponsor is entitled to an additional 6 months of exclusivity if it conducts a clinical study of the safety or effectiveness of its drug product in a

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* 21 USC § 355(q)(1)(G) (added by FDAAA).

† FDA October 28, 2008 "Dear ANDA Applicant" letter, Docket No. FDA-2008-N-0483 at 9. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2008-N-0483-0017. Accessed June 13, 2013 (involving dorzolamide/timolol).

‡ FDA September 11, 2009 "Dear Applicant" letter. Available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM182134.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=nateglinide%20180&utm_content=1. Accessed June 13, 2013 (involving nateglinide).

§ MMA § 1102(b)(2).

¶ FDA January 29, 2008 letter to Carmen Shepherd, et al., Docket No. FDA-2007-N-0035. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2007-N-0035-0004. Accessed June 13, 2013 (involving ramipril).

** 21 USC § 355(j)(5)(D)(i)(II).

†† 21 USC § 355(j)(5)(D)(i)(III).

‡‡ 21 USC § 355(j)(5)(D)(i)(VI).

pediatric population. The additional 6 months is added to the term of an unexpired Orange Book patent or 3-, 5-, or 7-year nonpatent exclusivity.*

One subject that has received attention is the effect of pediatric exclusivity on an ANDA or 505(b)(2) NDA sponsor's ability to receive final approval during the 6-month exclusivity period. The FDA has interpreted the arguably ambiguous statutory language so that the FDA cannot grant final approval during the 6-month pediatric exclusivity period to an applicant that had not received final approval before the underlying patent or exclusivity period expired. Thus, for example, an ANDA sponsor that had been blocked from receiving final approval by a Paragraph III patent certification† or by an unexpired 30-month litigation stay‡ cannot receive final approval until after the 6-month pediatric exclusivity period has run. Likewise, an ANDA sponsor that had received final approval but subsequently had its final approval converted to tentative approval status because of a loss in patent litigation is also precluded from receiving final approval during the pediatric exclusivity period.§ Although not all possible scenarios have been addressed by the FDA or the courts, it appears to this author that they would apply similar reasoning to prevent final approval until after the 6-month pediatric period has run.

As the result of a statutory change that applies to all pediatric study "written requests" issued by the FDA on or after September 27, 2007, pediatric exclusivity must now be awarded (if at all) at least 9 months before the expiration of the underlying nonpatent 3-, 5-, or 7-year exclusivity period or Orange Book patent that is to be extended.¶ Under prior law (which still applies to written requests issued before September 27, 2007), a qualifying study potentially could be submitted at any time before expiration of the underlying exclusivity period or patent. The FDA then had up to 90 days to determine whether the study qualified for an additional 6 months of exclusivity. During that 90-day time period, final approval of ANDAs and 505(b)(2) NDAs was blocked,** giving the innovator drug sponsor a de facto exclusivity period. (In practice, however, the de facto exclusivity period did not work to the disadvantage of most ANDA and 505(b)(2) NDA sponsors, as the FDA had granted pediatric exclusivity in most instances.)

By statute, the omission of patent- or exclusivity-protected pediatric use labeling information is expressly not a basis for refusing to approve an ANDA. The FDA is authorized to require the labeling of the generic product to include appropriate pediatric contraindications, warnings, or precautions as well as a statement that the drug product is not labeled for pediatric use.††

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* 21 USC § 355a (added by BPCA, amended by FDAAA).

† *Barr Laboratories, Inc. v. Thompson*, 238 F. Supp. 2d 236 (D.D.C. 2002) (involving tamoxifen).

‡ *Ranbaxy Laboratories Limited v. Food and Drug Administration*, 307 F. Supp. 2d 15 (D.D.C. 2004), affirmed 96 Fed. Appx. 1, 2004 WL 886333 (D.C. Cir. 2004) (involving fluconazole).

§ *Mylan Laboratories, Inc. v. Thompson*, 389 F. 3d 1272 (D.C. Cir. 2004) (involving fentanyl).

¶ 21 USC § 355a(c)(2).

** Former 21 USC § 355a(e) (amended by FDAAA).

†† 21 USC § 355a(o) (added by BPCA, recodified by FDAAA).

Antibiotics

At the time the Hatch–Waxman Amendments to the FDC Act were enacted in 1984, antibiotics were regulated under different provisions of the FDC Act than other pharmaceuticals. Those provisions already provided for ANDA-type abbreviated approvals. As a result, as enacted in 1984, Hatch–Waxman's ANDA procedure, Orange Book patent listing, patent certification, 30-month delay of ANDA final approval, and 3- and 5-year exclusivity provisions did not apply to antibiotic drugs. (However, the patent term restoration provisions in Title II of Hatch–Waxman did encompass antibiotics.)

In 1997, FDAMA repealed former Section 507 of the FDC Act concerning the approval of antibiotics.* Previously approved applications for antibiotics were to be treated as approved NDAs or ANDAs (depending on their form and content). By guidance, the FDA interpreted its new statutory provision so that any drug product containing an "old" antibiotic active ingredient that was the subject of an application received by the FDA before November 21, 1997, whether alone or with another active ingredient, would be regarded as an "old" antibiotic.†

In 2008, the FDC Act was further amended by the QI Act regarding "old" antibiotics.‡ Unfortunately, the statutory language is very confusing and capable of different interpretations. However, it appears that, at least on a going forward basis with regard to new NDAs submitted to the FDA after the enactment of the QI Act, this provision broadly extends longstanding Hatch–Waxman provisions to "old" antibiotics.§

DIFFERENCES BETWEEN INNOVATOR AND GENERIC PRODUCTS

ANDA Suitability Petitions

The Hatch–Waxman Amendments permit a generic drug product to differ from its brand-name counterpart in one or more of four regards if the difference is petitioned for and approved before ANDA submission.¶ These petitions, commonly known as ANDA suitability petitions, are submitted to the FDA using the format for a citizen petition and are, upon filing, in the public domain. For this reason, many prospective ANDA sponsors prefer to have petitions submitted for them by a consultant or law firm, on a "blind" basis.

The Hatch–Waxman Amendments permit ANDA suitability petitions for only four types of changes: dosage form, strength, route of administration, or active ingredient in a combination product. To date, more than 1000 ANDA suitability

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* FDAMA, § 125.

† *Guidance for Industry and Reviewers: Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*, May 1998. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080566.pdf. Accessed June 13, 2013.

‡ 21 USC § 355(v) (added by QI Act) and QI Act § 4(b) (setting forth transitional rules).

§ See FDA November 10, 2009 letter to Paul Rubin, FDA Docket No. FDA-2009-P-0225. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2009-P-0225-0007. Accessed June 13, 2013.

¶ 21 USC § 355(j)(2)(A)(ii) and (iii), and (j)(2)(C); 21 CFR § 314.93.

petitions have been submitted to the FDA.* The great majority of ANDA suitability petitions have sought changes in dosage form or strength. These petitions are routinely granted if the proposed modified generic drug appears to have a use that is consistent with the indications for use of the approved reference drug's labeling. A much smaller number of petitions have sought permission to file an ANDA for a new combination. In FDA's view, these petitions are appropriate only if the proposed change of active ingredient is the substitution of one active ingredient for another in the same pharmacologic or therapeutic class, such as the substitution of aspirin for acetaminophen in a combination product.† Most such petitions seeking a change in active ingredient have been denied, on the basis that the proposed change cannot be adequately evaluated in the context of an ANDA. Very few ANDA suitability petitions have been submitted seeking a new route of administration; these petitions have generally been denied on the basis that clinical studies are needed to evaluate the proposed modified product.

The FDA is required by the Hatch–Waxman Amendments to approve or disapprove an ANDA suitability petition within 90 days.‡ The first edition of this book noted that, although the FDA had generally not met that deadline, many decisions had been made within 6 months. Since then, FDA's delay in processing ANDA suitability petitions has lengthened substantially. Many petitions have languished for years.

If multiple ANDA sponsors submit ANDAs pursuant to an approved ANDA suitability petition, it is a "race to approval." The first ANDA approved becomes the reference product and sponsors of pending and future ANDAs must demonstrate bioequivalence against that product.§ Because an ANDA may not be amended to change the reference product,¶ the sponsor of any pending ANDA will have to submit a new ANDA.

A generic drug product authorized by an ANDA suitability petition will not be rated as therapeutically equivalent ("AB" or other "A" rating) to the innovator product upon which it is based in FDA's Orange Book. Thus, under the pharmacy laws of the great majority of states, no substitution at the pharmacy level is permitted. The lack of substitution at the pharmacy level may pose new sales and marketing challenges for many generic drug firms, as the new product will have to be "detailed" to physicians.

"Same" Active Ingredient

Except for the change authorized by an ANDA suitability petition of one active ingredient in a reference product with multiple active ingredients (see discussion in ANDA Suitability Petitions), the Hatch–Waxman Amendments require a generic

* ANDA suitability petitions filed after March 31, 1999 and their status is summarized in a chart on the FDA's website, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120944.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=anda%20suitability%20petition&utm_content=1. Accessed June 13, 2013.

† 21 CFR § 314.93(d).

‡ 21 USC § 355(j)(2)(C).

§ FDA November 25, 2008 letter to Mark Aikman, Docket No. FDA-2008-P-0329. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0329-0016. Accessed June 13, 2013 (involving venlafaxine).

¶ 21 USC § 355(j)(2)(D)(i) (as added by MMA).

product to have the "same" active ingredient as the innovator product upon which it is based.* Although the "sameness" of the active ingredient has generally not been a concern for chemically synthesized active ingredients, several challenges have been raised in connection with drug products of natural origin. The judicial decisions discussed below show that FDA has a large degree of discretion in this scientific area.

The D.C. Circuit concluded that the FDA has the scientific expertise and discretion to determine "sameness" for ANDA approval purposes; exact chemical identity is not required. For example, in a situation involving an active ingredient that is derived from natural sources, the FDA can reasonably conclude that the innovator and generic products have the "same" active ingredient, despite natural variations that lead to slightly different chemical side chains in different batches of the active ingredient.†

In a more recent matter, the district court upheld FDA's approval of an ANDA version of an innovator product that is not fully characterized. The district court also upheld FDA's authority to require the ANDA sponsor to submit immunogenicity test data, although such data are not expressly referenced in the statutory list of required information for an ANDA.‡

In an earlier matter, however, the FDA concluded that it could not approve generic products using chemically synthesized active ingredients based on an innovator product using naturally derived active ingredients.§ The FDA decided that it could not approve any generic version using chemically synthesized active ingredients until the active constituents of the innovator products have been better characterized and more information is available about them. Thus, although the innovator product has been marketed for two generations and relevant patents are long expired, it is not available for generic copying because the innovator drug sponsor has not sufficiently characterized its active constituents.

In general, the FDA regards different polymorphic forms of an active ingredient to be the "same" active ingredient. By guidance, the FDA has addressed polymorphism and its potential for affecting a generic product's bioavailability and bioequivalence.¶ In comparison, different salts, different esters, and other variations in the active ingredient result in a "different" active ingredient that cannot be addressed through the ANDA process. However, as discussed in 505(b)(2) NDAs below, a 505(b)(2) NDA may be appropriate for a "generic" product with such differences.**

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* 21 USC § 355(j)(2)(A)(ii).

† *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (involving menotropins).

‡ *Sanofi aventis U.S. LLC v. Food and Drug Administration*, 842 F. Supp. 2d 195 (D.D.C. 2012).

§ See 62 Fed. Reg. 42,562 (August 7, 1997) (involving conjugated estrogens).

¶ *Guidance For Industry—ANDAs: Pharmaceutical Solid Polymorphism, Chemistry, Manufacturing, and Controls Information*, July 2007. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072866.pdf. Accessed June 13, 2013.

** The FDA has recognized that the use of a 505(b)(2) NDA where the only difference from the reference product is a change in the form of the active ingredient, such as a change in salt, arguably undermines 180-day exclusivity and causes confusion in the marketplace. The FDA stated it is reserving these issues for future review. FDA October 14, 2003 letter to Katherine Sanzo et al., at 33-34, Docket No. FDA-2003-P-0274. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2003-P-0274-0015. Accessed June 13, 2013.

"Same" Dosage Form

Except for changes authorized by the granting of an ANDA suitability petition, the Hatch–Waxman Amendments require a generic product to be in the "same" dosage form as the innovator product upon which it is based.* The FDA's list of "Uniform Terms" for dosage forms of currently marketed products appears in Appendix C of the Orange Book.

Although several innovator firms have challenged ANDA approval decisions based on apparent distinctions between dosage forms, the FDA and the courts have had little difficulty disposing of these challenges. FDA's decision that a generic product using conventional extended-release tablet technology was the "same" dosage form as the innovator product using patented osmotic pump extended-release tablet technology for ANDA approval purposes was upheld.† Similarly, the courts have upheld FDA's determination that a generic drug product described as a tablet inside a gelatin capsule was the "same" dosage form as the innovator's capsule.‡

The statutory provision added to the FDC Act by the PREA that requires pediatric clinical studies may create an obstacle to obtaining approval of new dosage forms. This provision requires the sponsor of an application seeking approval for, in relevant part, a new dosage form of an approved drug product to provide data regarding the safety and effectiveness of the proposed drug product in pediatric subpopulations.§ The pediatric studies requirement can be waived by the FDA, in whole or in part, for several reasons, including if the proposed drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.¶

"Same" Labeling

Except for differences related to the identification of the different firms involved or changes authorized by the granting of an ANDA suitability petition, the Hatch–Waxman Amendments require the labeling of the proposed generic product to be the "same" as the labeling of the innovator product.**

FDA's decision to approve a generic version of a parenteral innovator product, with a different preservative and slightly different labeling, was upheld in a judicial challenge. The innovator product contained the preservative disodium edentate (EDTA) to prevent microbial contamination. The FDA approved a generic version of the product with sulfite as the preservative rather than EDTA. Because some individuals are allergic to sulfite, the labeling of the generic product included a sulfite warning. The innovator firm challenged the ANDA approval, on the basis that the generic product did not have the "same" labeling as the innovator. The court rejected

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* 21 USC § 355(j)(2)(A)(iii).
† *Pfizer Inc. v. Shalala*, 182 F.3d 975 (D.C. Cir. 1999) (involving nifedipine).
‡ *Warner-Lambert Company v. Shalala*, 202 F.3d 326 (D.C. Cir. 2000) (involving phenytoin sodium).
§ 21 USC § 355c (as added by the PREA and amended by the FDAAA).
¶ 21 USC § 355c(b)(2).
** 21 USC § 355(j)(2)(A)(v).

that contention, ruling that FDA's decision to allow the sulfite warning was entitled to substantial deference.*

The Hatch–Waxman Amendments permit an ANDA to omit an indication or other aspect of labeling that is protected by a patent or by exclusivity. This subject is discussed in Three-Year Exclusivity for Product "Improvements."

A provision added to the FDC Act in 2010 prevents, in most situations, changes to the labeling of the innovator product within 60 days of the anticipated date of generic competition from blocking generic competition.† An ANDA sponsor can receive approval based on "old" labeling, based on a commitment to submit revised labeling within 60 days. This exception does not apply if the change is to the "Warnings" section of the innovator's product labeling or if FDA determines that the "old" labeling raises a safety issue. The FDA has used this authority on several occasions.‡

In 2011, the US Supreme Court effectively foreclosed most state law product liability "failure to warn" lawsuits against generic drug companies.§ The Supreme Court held that, because generic drug products must use the "same" labeling as the innovator products being copied, generic manufacturers have no ability to revise their labeling. The result is that state laws imposing a "duty to warn" are preempted because compliance with both federal law and state law is impossible. Legislative action in this area is possible.

Bioequivalency

As enacted in 1984, the Hatch–Waxman Amendments defined bioequivalency solely in terms of the rate and extent of absorption of the innovator and proposed generic products.¶ Nevertheless, on several occasions, the courts upheld FDA decisions to permit alternative means of establishing bioequivalence for nonsystemically absorbed drug products.** In 2003, the MMA amended the definition of bioequivalency to provide the FDA with express authority to determine scientifically valid assessments of bioequivalency for nonsystemically absorbed drug products.††

Other FDA decisions regarding bioequivalency have also been upheld by the courts. For example, in upholding FDA's decision to rely on an assay for the metabolite rather than the parent drug itself in assessing bioequivalency, one court concluded that the appropriate method to be used for determining bioequivalency is a matter of scientific judgment, squarely within FDA's discretion.‡‡ Another court

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* *Zeneca, Inc. v. Shalala*, 213 F.3d 161 (4th Cir. 2000) (involving propofol).

† 21 USC § 355(j)(10) (added by Pub. L. No. 111-148).

‡ E.g., FDA November 26, 2010 approval letter to Ranbaxy Inc. for donepezil hydrochloride tablets. Available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/076786s000ltr.pdf. Accessed June 13, 2013.

§ *Pliva, Inc. v. Mensing*, 131 S. Ct. 2568 (2011).

¶ Former 21 USC § 355(j)(8) (amended by MMA).

** *Fisons Corporation v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994) (involving cromolyn sodium for inhalation); *Bristol-Myers Squibb Company v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996) (involving cholestyramine); *Schering Corp. v. Food and Drug Administration*, 51 F.3d 390 (3rd Cir. 1995) (involving inhalation and topical drug products).

†† 21 USC § 355(j)(8) (as amended by MMA).

‡‡ *Somerset Pharmaceuticals, Inc. v. Shalala*, 973 F. Supp. 443, 453 (D. Del. 1997) (involving selegiline).

rejected a challenge to FDA's decision that the ANDA product only had to be shown to be bioequivalent to the reference product being copied, not to predecessor versions of the reference product mentioned in the innovator product's labeling.* With this history of judicial deference to FDA's interpretation of bioequivalence, it seems relatively unlikely that a successful challenge to FDA decisions in this area will be mounted in the future.

An increasing number of innovator drugs that pose special risks are being approved with limited distribution systems under FDA's authority to impose Risk Evaluation and Mitigation Strategies (REMS),† discussed in Risk Evaluation and Mitigation Strategies below. Some innovator companies have used limited distribution procedures as a basis for refusing to sell product samples to would-be ANDA sponsors, thereby blocking generic competition. Legislation may be necessary to resolve this matter.

Prescription-to-OTC Switches

The innovator sponsor's decision to switch its drug product from prescription to over-the-counter (OTC) status could present additional obstacles to generic firms. If the supplemental NDA providing for OTC labeling is supported by essential clinical studies, the innovator firm is entitled to 3 years of exclusivity during which no ANDA could be approved. Moreover, under FDA policy, an ANDA or 505(b)(2) NDA could no longer be approved based on the previously approved prescription labeling.‡

Even if the innovator is not entitled to exclusivity, a prescription-to-OTC switch near the date of the innovator's patent expiration is likely to cause some delays in ANDA approvals, as generic firms would be required to create, and obtain FDA approval for, new labeling and packaging. If the innovator product were switched to OTC status after final ANDA approval, the FDA would presumably give the ANDA sponsor a reasonable length of time to supplement its approved ANDA to provide for an OTC product. However, if the innovator firm received 3-year exclusivity, the generic firm would be forced off the market until exclusivity expiration, despite having an approved ANDA for a prescription product. Finally, the marketing and distribution of an OTC product could present new challenges for many generic firms that have no experience competing in this market, which is dominated by private label products marketed by large retail pharmacy chains.

505(b)(2) NDAs

Section 505(b)(2) of the FDC Act, added as part of the Hatch–Waxman Amendments, authorizes an NDA where some of the safety or effectiveness investigations required to support NDA approval were not conducted for the applicant, and for which the applicant has not obtained a right of reference or use.§ A 505(b)(2) NDA is, in essence,

* *Biovail Corporation v. U.S. Food and Drug Administration*, 519 F. Supp. 2d 39 (D.D.C. 2007) (involving bupropion).
† 21 USC § 355-1(f) (added by FDAAA).
‡ 21 CFR § 310.200(d).
§ 21 USC § 355(b)(2).

a hybrid that includes elements of a complete (or "full") NDA as well as an ANDA. A 505(b)(2) NDA must include, in some manner, all of the elements required for a complete NDA, including full safety and effectiveness data. However, a 505(b)(2) NDA sponsor does not own, or have a right of reference to, some of the required data package. Thus, a 505(b)(2) NDA typically relies, in substantial part, on published literature, FDA's decision to approve a similar drug product, or both.

A 505(b)(2) NDA is subject to the same Hatch–Waxman constraints on approval as an ANDA, except for 180-day exclusivity. Thus, a 505(b)(2) NDA must address all relevant patents in the Orange Book, is subject to a delay of final approval in the event of Paragraph IV patent litigation, and is subject to 3-, 5-, and 7-year and 6-month exclusivity. A 505(b)(2) NDA is not eligible for, and is not affected by, 180-day exclusivity. In keeping with its hybrid status, a 505(b)(2) NDA sponsor (unlike an ANDA sponsor) also has an obligation to list relevant patents in the Orange Book. A 505(b)(2) NDA sponsor can earn its own 3- or 5-year exclusivity, which in turn prevents FDA final approval or acceptance of competing ANDAs and 505(b)(2) NDAs. These matters are discussed in greater detail below.

FDA regulations and guidance documents provide relatively little meaningful information regarding substantive issues related to 505(b)(2) NDAs. Although the FDA has been the subject of several legal challenges involving 505(b)(2) NDAs, none of these cases resulted in a meaningful substantive decision. Thus, the best sources of information regarding FDA's interpretation of the 505(b)(2) NDA provisions of the FDC Act are FDA's decisions to a number of citizen petitions* and its approval decisions.

In general, the FDA has interpreted the permissible scope of 505(b)(2) NDAs broadly, rejecting industry suggestions that they should be limited to the equivalent of old "paper NDAs."†

Regarding patent certifications, FDA's view is that a 505(b)(2) NDA sponsor should choose the listed drug or drugs that are most similar to the proposed drug product and that a 505(b)(2) NDA sponsor should address only those patents listed in the Orange Book for approved products on whose finding of safety and effectiveness the FDA would need to rely for approval. A 505(b)(2) NDA sponsor need not address patents listed in connection with NDAs on which the FDA could have relied but did not in fact rely. Where a 505(b)(2) NDA seeks to rely on FDA's approval of a drug that is itself the subject of a 505(b)(2) NDA, the 505(b)(2) NDA applicant should certify to any patents that the earlier 505(b)(2) NDA sponsor relied on as well as to

* FDA October 14, 2003 letter to Katherine Sanzo et al., Docket No. FDA-2003-P-0274 available at http://www.regulations.gov/#!documentDetail;D=FDA-2003-P-0274-0015. Accessed June 13, 2013; FDA August 12, 2005 letter to Nancy Buc et al., Docket No. FDA-2004-P-0003 available at http://www.regulations.gov/#!documentDetail;D=FDA-2004-P-0003-0003. Accessed June 13, 2013; FDA May 30, 2006 letter to Kathleen Sanzo et al., Docket No. FDA-2004-P-0339 available at http://www.regulations.gov/#!documentDetail;D=FDA-2004-P-0339-0003. Accessed June 13, 2013; FDA November 30, 2004 letter to Donald Beers et al., Docket No. FDA-2004-P-0089 available at http://www.regulations.gov/#!documentDetail;D=FDA-2004-P-0089-0003. Accessed June 13, 2013; FDA May 25, 2011 letter to Gary Veron et al., Docket No. FDA-2010-P-0614 (available at http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0614-0072. Accessed June 13, 2013 (involving colchicine).

† FDA Oct. 14, 2003 letter, *supra,* n. *.

any patents of the underlying NDA on which that earlier 505(b)(2) NDA relied for approval.*

On rare occasion, a 505(b)(2) NDA can qualify for 5-year NCE exclusivity.† More likely, a 505(b)(2) NDA will qualify for 3-year "new clinical studies" exclusivity, based on new clinical studies (other than bioequivalence studies) conducted for the applicant that are essential to the approval of the application. Typically, only the first 505(b)(2) NDA approved for a "change" can receive 3-year exclusivity, as clinical studies that support later applications are deemed to be "not essential" for approval. The first 505(b)(2) NDA sponsor to receive approval for a "change" typically receives 3-year exclusivity that blocks the approval of then-pending 505(b)(2) NDAs seeking the same or a similar "change" regardless of when those other 505(b)(2) NDAs were submitted. Thus, 3-year exclusivity for 505(b)(2) NDAs creates a "race to approval." A 505(b)(2) NDA entitled to 3-year exclusivity blocks the approval of another 505(b)(2) NDA "for the conditions of approval" of the drug entitled to 3-year exclusivity.‡ There does not appear to be a definitive FDA interpretation regarding the circumstances under which 3-year exclusivity blocks the final approval of a similar 505(b)(2) NDA.

A 505(b)(2) NDA sponsor's exclusivities block ANDAs and 505(b)(2) NDAs (subject to the uncertainties discussed above) but do not block a "full" 505(b)(1) NDA (where the NDA sponsor owns or has the right of reference to all data needed for approval).

A 505(b)(2) NDA may be the preferred vehicle for seeking FDA approval in a number of situations. On relatively rare occasion, a 505(b)(2) NDA can be used to obtain the first FDA approval for a drug that has a history of use in other countries and is the subject of published reports in scientific literature; in these situations, a 505(b)(2) NDA can earn 5-year exclusivity.§ Much more commonly, a 505(b)(2) NDA can be used to pursue FDA approval for active ingredient changes that are not permitted for an ANDA, such as a different salt, ester, racemate, or enantiomer of the active ingredient, changes in dosing regimen, and changes in indication. A 505(b)(2) NDA may be suited for modified "generic" versions of innovator products, such as extended- or delayed-release versions of regular-release innovator products. Other examples of products amenable to the 505(b)(2) NDA process include combination products, prescription-to-OTC switches, and new inactive ingredients that require clinical study.

A 505(b)(2) NDA may also be appropriate for changes that in theory could be addressed through the ANDA suitability petition process, but the FDA has generally indicated that clinical studies are needed to support the approval, such as changes in the route of administration. FDA's regulations provide that the agency "may" refuse to accept a 505(b)(2) NDA for a "duplicate" product that can be addressed through an ANDA,¶ and the FDA has recently enforced this provision.**

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* FDA Nov. 30, 2004 letter, *supra*, n. *, p. 353.

† E.g., FDA approvals of Thalomid® (thalidomide) and Radiogardase® (ferric hexacyanoferrate (II)).

‡ 21 USC § 355(c)(3)(E)(iii).

§ See examples in n. †.

¶ 21 CFR § 314.101(d)(9).

** FDA May 25, 2011 letter, *supra*, n. *, p. 353.

In situations where the sponsor of a 505(b)(2) NDA seeks to rely on FDA's finding of finding and effectiveness for a previously approved drug product, the 505(b)(2) NDA sponsor must establish an appropriate scientific basis for that reliance. In many cases, this reliance can be justified based on "bridging" studies, often consisting of bioavailability and/or bioequivalence studies.* In addition, one or more clinical studies may be necessary to demonstrate that the proposed product is safe and effective.

Although, in theory, an ANDA can be based on any innovator product that was approved under an NDA, special hurdles exist for biological-type drug products and recombinant protein products, such as human growth hormone and insulin. These problems stem from the inherently variable nature of these products. The FDA has to date taken the position that it will not approve an ANDA for a generic version of these products because it cannot evaluate these products adequately under the Hatch–Waxman ANDA provisions; however, a 505(b)(2) NDA may be appropriate. A synthetic version of a naturally derived innovator product approved through a 505(b)(2) NDA could be regarded as having a different active ingredient than the innovator product,† meaning it cannot be rated as therapeutically equivalent.

A 505(b)(2) NDA may be appropriate for drug products that present bioequivalence difficulties, where it may be preferable to conduct a clinical trial to assess product comparability rather than a traditional bioequivalence trial. Such a drug product approved through a 505(b)(2) NDA is not automatically rated as therapeutically equivalent to its brand-name counterpart and thus could not be substituted for the innovator product by a pharmacist under typical state pharmacy laws. It may be necessary to "detail" such a product to physicians, thereby creating new marketing hurdles for some generic firms. However, where the innovator and 505(b)(2) NDA products are regarded by the FDA as "pharmaceutically equivalent" (same active ingredient, dosage form, route of administration, and strength/concentration), it may be possible to conduct additional testing to demonstrate bioequivalence and therapeutic equivalence with the innovator product.

PATENT-RELATED ISSUES

Scope of Hatch–Waxman Patent Listing Provisions

The Hatch–Waxman Amendments require each NDA sponsor to submit for Orange Book listing "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."‡ If such a patent issues after the NDA is approved, patent information must be submitted to the FDA within 30 days after patent issuance.§

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* FDA August 12, 2005 letter, *supra*, n. *, p. 353.

† *Compare* Premarin® ("conjugated estrogens") *with* Cenestin® ("synthetic conjugated estrogens, A"). See n. §, p. 349, *supra*.

‡ 21 USC § 355(b)(1).

§ 21 USC § 355(c)(2).

In its 1994 implementing regulation, the FDA interpreted these provisions to provide for the listing of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. Drug substance patents are eligible for listing only if they claim a "component" of the approved drug product, and drug product patents are eligible for listing only if they claim an approved drug product. The method-of-use patents are eligible for Orange Book listing only if they claim approved indications or other conditions of use. Process patents are not eligible for Orange Book listing.* In connection with each formulation, composition, or method-of-use patent submitted for Orange Book listing—but not for drug substance patents—the NDA sponsor must submit a declaration that the patent "covers the formulation, composition, and/or method of use" of the drug product for which approval is being sought or which has been approved.†

Considerable controversy surrounded the appropriate interpretation of FDA's 1994 patent listing regulation. Innovator drug firms had increasingly interpreted FDA's patent listing regulation to their benefit, and considerable litigation resulted. Several courts upheld FDA's longstanding view that its role in patent listings was ministerial, so that the agency could not be sued for improperly listing a patent.‡

In 2001, the Federal Circuit decided that an ANDA sponsor could not sue an NDA sponsor seeking the delisting of an Orange Book patent.§ In response to this decision, the FDC Act was amended in 2003 by the MMA so that an ANDA or 505(b)(2) NDA sponsor that is sued for patent infringement pursuant to a Paragraph IV certification can bring a counterclaim seeking delisting of the patent, on the basis that the patent does not claim the approved drug or a method of using the approved drug. No damages are available on a counterclaim, and an independent cause of action for patent delisting is expressly not authorized.¶

In 2003, the FDA made substantial revisions to its patent listing regulation.** The current requirements, which (except as otherwise indicated) apply to patents submitted to the FDA for Orange Book listing on or after August 18, 2003, prohibit the submission of patents claiming packaging (e.g., bottles or containers), intermediates, and metabolites of the active ingredient. The FDA clarified that product-by-process patents are eligible for Orange Book listing.†† Effective December 18, 2003, patents claiming a different polymorphic form of the active ingredient (different crystalline structures, different waters of hydration, solvates, and amorphous forms) in the approved drug product must be submitted for listing if the NDA sponsor has test data to demonstrate the "sameness" of the different polymorphic forms. The FDA adopted detailed declarations to be used as "checklists" for the submission of patent information, with the goal of ensuring only appropriate patents are listed in the Orange Book. For method-of-use patents, the NDA sponsor must identify specific patent claims relevant to the NDA and submit specific use code language for Orange

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* Former 21 CFR § 314.53(b).

† Former 21 CFR § 314.53(c)(2).

‡ *Teva Pharmaceuticals*, *supra*, n. ‡, p. 343.

§ *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001) (involving buspirone).

¶ 21 USC § 355(j)(5)(C)(ii) and (c)(3)(D)(ii) and (iii) (as amended by MMA).

** 21 CFR § 314.53 (as amended by 68 Fed. Reg. 36,675 (June 18, 2003)).

†† 68 Fed. Reg. at 36,679.

Book publication. The submission to the FDA of an allegedly incorrect patent use code is within the scope of the delisting counterclaim provision discussed above.*

It appears that FDA's 2003 revision of its patent listing regulation has addressed many prior problems with regard to the scope of patents submitted to the FDA for Orange Book listing. However, there remain a considerable number of patents submitted to the FDA for listing under FDA's prior regulation, some of which apparently would not qualify for listing under FDA's current criteria. NDA sponsors have in recent years asked the FDA to "delist" a number of Orange Book patents. These actions may have been founded, at least in part, on concerns about possible antitrust liability stemming from improperly listed patents.

30-Month Delay of ANDA and 505(b)(2) NDA Final Approval

The Hatch–Waxman Amendments provide that ANDA or 505(b)(2) NDA final approval is automatically delayed by 30 months following a Paragraph IV certification to an Orange Book patent, notice of the certification to the NDA sponsor and patent holder, and the timely filing of a Hatch–Waxman patent infringement lawsuit within 45 days of receipt of the notice. The 30-month delay period terminates if the ANDA or 505(b)(2) NDA sponsor obtains a court decision (including a district court decision) that the patent is invalid or not infringed, or there is a settlement order or consent decree signed by the court stating that the patent is invalid or not infringed.† Only a favorable court decision involving an ANDA or 505(b)(2) NDA sponsor will terminate that sponsor's 30-month delay period. A decision in litigation involving a different applicant that the patent is invalid or not infringed does not automatically terminate a sponsor's 30-month delay period.

In a situation where a Paragraph IV ANDA or 505(b)(2) NDA is filed on or after the NCE-1 date (4 years into the innovator product's 5-year NCE exclusivity period, discussed in Five-Year New Chemical Entity Exclusivity), the delay of final approval lasts until 7.5 years after approval of the innovator product.‡ Thus, in practice, the period during which final approval of the ANDA or 505(b)(2) NDA is delayed could be as long as 42 months.

The 30-month period can the lengthened or shortened by the court hearing the patent case "because either party to the action failed to reasonably cooperate in expediting the action."§ One district court's decision to shorten the 30 months, based on what it viewed as the NDA sponsor's improper conduct before the FDA in connection with the listing of the patent, was rejected on appeal by the Federal Circuit. The Federal Circuit concluded that the 30-month period could be shortened based only on delay related to the particular infringement lawsuit.¶

In 2003, the FDC Act was amended to provide that, in most cases, the 30-month stay of final ANDA or 505(b)(2) NDA approval is available only with regard to

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* *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670 (2012) (involving repaglinide).

† 21 USC § 355(c)(3)(C) and (j)(5)(B)(iii) (as amended by MMA).

‡ 21 USC § 355(c)(3)(E)(ii) and (j)(5)(F)(ii) (as amended by MMA).

§ 21 USC § 355(c)(3)(C) and (j)(5)(B)(iii).

¶ *Andrx Pharmaceuticals, Inc. v. Biovail Corp.*, 276 F.3d 1368, 1376 (Fed. Cir. 2002) (involving diltiazem).

patents that were listed in the Orange Book before submission of the ANDA or 505(b)(2) NDA.* This provision applies to patents listed in the Orange Book on or after August 18, 2003.† The practical result is that there is, in most cases, a single 30-month stay per ANDA or 505(b)(2) NDA. A notable exception is where the ANDA or 505(b)(2) NDA sponsor initially submits a Paragraph III certification to a patent listed in the Orange Book at the time of original application submission but subsequently converts its Paragraph III certification to a Paragraph IV certification.‡

Hatch–Waxman Patent Infringement Litigation

Under the current interpretation of 180-day generic drug exclusivity, 180-day exclusivity is available whenever a Paragraph IV ANDA is filed. Although a discussion of patent infringement litigation is beyond the scope of this book, two brief points are worthy of note.

First, the sponsor of a Paragraph IV ANDA always stands a reasonably likelihood of being sued for patent infringement in the Hatch–Waxman 45-day window. Although ANDA sponsors may, as a matter of business tactics, want to be aggressive in filing Paragraph IV ANDAs and pursuing patent challenges, the merit—or lack of merit—of any particular challenge should be viewed objectively. Paragraph IV ANDA applicants have been found liable for the NDA sponsor's and patent holder's very substantial attorneys' fees for pursuing what the court characterized as baseless patent challenges.§ In such cases, attorneys' fees often amount to millions of dollars.

Second, in some cases, Paragraph IV ANDA applicants have been sued, within the Hatch–Waxman 45-day window, for infringement of patents not listed in the Orange Book. The Federal Circuit ruled that a patent holder could seek a declaratory judgment that its process patent (which is not eligible for Orange Book listing) will be infringed by the ANDA sponsor.¶ In other cases, Paragraph IV ANDA applicants were sued, again within the 45-day Hatch–Waxman window, for alleged infringement of, and inducement to infringe, Orange Book method-of-use patents claiming unapproved uses. The Federal Circuit has affirmed district court decisions granting summary judgments of noninfringement in such cases.**

Declaratory Judgment Actions

Since the enactment of the Hatch–Waxman Amendments in 1984, ANDA and 505(b)(2) NDA sponsors have been able to bring a declaratory judgment action seeking

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* 21 USC § 355(c)(3)(C) and (j)(5)(B)(iii) (as amended by MMA).

† MMA § 1101(c)(3).

‡ *Draft Guidance for Industry: Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch–Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Questions and Answers*, October 2004. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072887.pdf. Accessed June 13, 2013.

§ E.g., *Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.*, 549 F.3d 1381 (Fed. Cir. 2008) (upholding award of $16.8 million in attorneys' fees in connection with pioglitazone).

¶ *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570-71 (Fed. Cir. 1997) (involving ranitidine).

** E.g., *Warner-Lambert Company v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003) (involving gabapentin).

a declaration of patent invalidity, noninfringement, or unenforceability once the 45-day window for a patent infringement lawsuit has run and no suit was brought.* A successful declaratory judgment action can help bring patent certainty, as a patent owner can bring a patent infringement lawsuit after a generic sponsor receives final approval and begins marketing even if the patent owner had elected not to bring a patent infringement lawsuit pursuant to notice of a Paragraph IV certification. For a "subsequent" Paragraph IV ANDA sponsor that is blocked by the first-filer's 180-day exclusivity, a successful declaratory judgment lawsuit can trigger (or help trigger) the first filer's 180-day exclusivity.

The MMA added a condition precedent to the bringing of a declaratory judgment lawsuit seeking a declaration of patent noninfringement. Before an ANDA or 505(b)(2) NDA sponsor can bring such a declaratory judgment action, it must make an offer of confidential access to its pending application. The offer of confidential access is to be part of the notice of a Paragraph IV certification given to the NDA sponsor and the patent owner.†

The MMA also amended patent law to provide that the courts "shall, to the extent consistent with the Constitution, have subject matter jurisdiction" over declaratory judgment actions regarding patents.‡

The existence (or lack thereof) of subject matter jurisdiction over declaratory judgment lawsuits involving Orange Book patents has been a source of substantial controversy. The Federal Circuit has held that the courts may have jurisdiction over a declaratory judgment lawsuit based on an Orange Book patent that was not the subject of a Paragraph IV patent infringement lawsuit.§ However, there is no jurisdiction if the declaratory judgment plaintiff has stipulated to the validity and noninfringement of an Orange Book patent that blocks generic competition.¶ A covenant not to sue granted to the declaratory judgment plaintiff by the patent owner does not automatically defeat declaratory judgment jurisdiction.** In the author's view, there is room for interpretation as district courts continue to apply these Federal Circuit decisions to specific factual scenarios.

Bolar-Type Considerations

The Hatch–Waxman Amendments permit an ANDA or 505(b)(2) NDA sponsor or prospective sponsor to engage in activities reasonably related to seeking government approval for its generic drug, without infringing any patents covering the innovator drug.†† This provision is commonly known as the Bolar provision. Because the FDA requires validation data from three commercial-size manufacturing batches as a

* 21 USC § 355(c)(3)(D)(i) and (j)(5)(C)(i) (as amended by MMA).
† 21 USC § 355(c)(3)(D)(i)(III) and (j)(5)(C)(i)(III) (as added by MMA).
‡ 35 USC § 271(e)(5) (as added by MMA).
§ *Teva Pharmaceuticals USA, Inc. v. Novartis Pharmaceuticals Corporation*, 482 F. 3d 1330 (Fed. Cir. 2007) (involving famciclovir).
¶ *Janssen Pharmaceutical, N.V. v. Apotex, Inc.*, 540 F.3d 1353 (Fed. Cir. 2008) (involving risperidone).
** *Caraco Pharmaceutical Laboratories, Ltd. v. Forest Laboratories, Inc.*, 527 F.3d 1278 (Fed. Cir. 2008) (involving escitalopram).
†† 35 USC § 271(e)(1).

condition of ANDA or 505(b)(2) NDA approval, the Hatch–Waxman Bolar provision effectively permits an ANDA or 505(b)(2) NDA sponsor to stockpile reasonable quantities of product for product launch in anticipation of final approval. However, it does not provide a safe harbor from infringement for any additional product manufactured before final approval. Likewise, there is no safe harbor from infringement of patents covering equipment or products that may be related to product development but that are not of themselves subject to the FDA approval process.* To the extent that an ANDA or 505(b)(2) NDA sponsor's proposed product is developed or manufactured in a foreign country, differing patent laws will apply and there may be no safe harbor.

AUTHORIZED GENERICS

An authorized generic is a drug product approved under the innovator firm's NDA but marketed through generic marketing channels in generic trade dress rather than under the innovator's brand name. Authorized generics are sometimes marketed by a subsidiary of the innovator drug company; more often, they are marketed by an independent company pursuant to a contract between that company and the innovator company. In some cases, an authorized generic results from the settlement of Paragraph IV patent infringement litigation, whereby the generic company entitled to 180-day exclusivity rights for that drug product receives the right to market an authorized generic version of the product, typically starting 6 months or so before patent expiration. In other instances, the innovator company has entered into an agreement for marketing and distribution of an authorized generic version of its product to coincide with the commercial launch of a "true" (ANDA) generic.

Authorized generics are a definite source of controversy between different industry segments. The innovator industry and some segments of the generic industry generally contend that authorized generics give consumers more choice and save money, by leading to competition in the "generic" marketplace sooner. For example, the availability of an authorized generic at the time that a true generic is launched will typically result in lower prices, as it is well recognized that the price of generic products decreases as the number of marketplace competitors increases. Not surprisingly, many segments of the generic industry generally take a different view. These segments of the generic industry contend that the real underlying purpose of authorized generics is to reduce or destroy the value of the 180-day exclusivity incentive, thereby undermining and devaluing the entire incentive for challenging patents on innovator drug products. In several lawsuits against the FDA, generic companies have asserted that authorized generics are unlawful. However, these lawsuits have been rejected by two Courts of Appeals.†

Agreements between innovator drug companies and Paragraph IV ANDA sponsors that concern, among other matters, authorized generics have to be reported to

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* *Proveris Scientific Corporation v. Innovasystems, Inc.*, 536 F.3d 1256 (Fed. Cir. 2008).

† *Teva Pharmaceutical Industries Ltd. v. Crawford*, 410 F.3d 51 (D.C. Cir. 2005) (involving gabapentin); *Mylan Pharmaceuticals, Inc. v. Food and Drug Administration*, 454 F.3d 270 (4th Cir. 2006) (involving nitrofurantoin).

the FTC and the Department of Justice, as discussed in Antitrust Considerations below. As required by the FDC Act,* the FDA has established an Internet database of all authorized generic drugs known to FDA.† To provide information for that database, NDA sponsors are required to include information about authorized generics in their annual reports.‡

If a Paragraph IV ANDA sponsor entitled to 180-day exclusivity launches an authorized generic, that launch starts the 180-day exclusivity period.§

BIOSIMILARS

As enacted in 1984, the abbreviated approval and nonpatent exclusivity provisions of the Hatch–Waxman Amendments do not apply to biological products licensed by the FDA under the Public Health Service Act. (However, biological products are within the scope of the patent term restoration provisions of Title II of the Hatch–Waxman Amendments.) In 2010, following years of debate, the BPCIA amended the Public Health Service Act to establish a regulatory pathway for the approval of abbreviated applications for biosimilar biological products. The new regulatory pathway includes both substantial similarities to, and differences from, the ANDA and 505(b)(2) NDA approval pathways established by the Hatch–Waxman Amendments.

To be eligible for approval, an abbreviated application has to establish that the proposed product is "biosimilar" to an approved reference product. That showing must be based on data derived from analytical studies, animal studies, and one or more clinical studies. Minor differences in clinically inactive components of the proposed and reference products are permitted. If the mechanism or mechanisms of action are known for the reference product, the proposed biosimilar product has to utilize the same mechanism or mechanisms of action. The proposed biosimilar product has to have the same indications for use, route of administration, dosage form, and strength as the licensed reference product.¶ A proposed biosimilar product could be licensed as "interchangeable" based on an additional showing that it can be expected to produce the same clinical result as the reference product.**

The regulatory pathway includes provisions that provide for the exchange of information relating to patents on the licensed reference product, including an opportunity for patent infringement litigation if the matter cannot be resolved. Unlike the ANDA and 505(b)(2) provisions of the FDC Act, the biosimilars provisions do not provide for any delay in FDA licensure; rather, it is up to the patent owner to seek an injunction to prevent the commercial marketing of a biosimilar product.††

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* 21 USC § 355(t) (as added by FDAAA).

† Available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm126391.htm. Accessed June 13, 2013.

‡ 21 CFR § 314.3(b) and § 314.81(b)(2)(ii)(b) (73 Fed. Reg. 56,487; September 29, 2008).

§ 21 USC § 355(j)(5)(B)(iv)(I) (as amended by MMA) (for ANDAs subject to 180-day forfeiture requirements added by MMA); *Mylan Pharmaceuticals, Inc. v. Thompson*, 207 F. Supp.2d 476, 488 (N.D. W.Va. 2001) (for pre-MMA ANDAs).

¶ 42 USC § 351(k)(2)(A).

** 42 USC § 351(k)(2)(B).

†† See 42 USC § 262(l).

An application for a biosimilar cannot be approved in the first 12 years after the initial licensure of a reference product; an application cannot be filed with the FDA during the first 4 years after the first licensure of the reference product.* Roughly comparable with 180-day exclusivity for generic drug products approved under an ANDA, the first interchangeable biosimilar receives a period during which other interchangeable biosimilars cannot be approved.†

In February 2012, a draft guidance on biosimilars was issued.‡ Early approvals for biosimilars are likely to consist of therapeutic protein products, typically produced through biotechnology. On the grand scale of all biologics, these products are "simple" biologics. At this time, "traditional" biologics, such as blood and blood products and vaccines, are far too complex to be candidates for the biosimilar approval mechanism. Likewise, so-called "frontier" biologics, such as cell-based treatments and gene therapy, are unlikely candidates.

At the time of this writing, user fee legislation for biosimilars is likely to be enacted; the user fee program would start with fiscal year 2013 (beginning October 1, 2012).

MISCELLANEOUS

Withdrawal of Approval of Innovator Drug

The Hatch–Waxman Amendments provide that an ANDA may be based on an innovator drug that is no longer marketed, provided the innovator drug was not withdrawn from sale for safety or effectiveness reasons.§ An ANDA sponsor that wants to base its product on a discontinued innovator drug must petition the FDA to make a determination that the product was not discontinued for safety or effectiveness reasons.¶ In addition, an ANDA may not be based on an innovator product for which the FDA has begun the formal administrative process to withdraw NDA approval for safety or effectiveness reasons.**

The withdrawal of approval of the innovator product upon which an ANDA is based can present special obstacles. In one case, the approved innovator product was in tablet form. Less than 1 month before the expiration of nonpatent exclusivity on the innovator product, the innovator firm obtained FDA approval for a capsule form of its drug product. It then discontinued the tablet form and attempted to attribute a safety reason for this decision: prevention of counterfeit versions of its tablet product and the elimination of mix-ups of the tablet product with similar appearing drug products. Thereafter, the FDA determined that the innovator tablet product had not been withdrawn for safety or effectiveness reasons. This determination

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* 42 USC § 262(k)(7).

† 42 USC § 262(k)(6).

‡ *Draft Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biosimilars Price Competition and Innovation Act of 2009*, February 2012. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf. Accessed June 13, 2013.

§ 21 USC § 355(j)(4)(I).

¶ 21 CFR § 314.122.

** 21 USC § 355(j)(4)(I).

allowed ANDA sponsors to seek approval for generic version of the tablet product, although the innovator tablet product was no longer being marketed. FDA's decision was upheld by a court, which stated that FDA's determination that the withdrawal was not for safety or effectiveness reasons was, in the first instance, within FDA's discretion.*

"Moving Target" and Disagreements with the FDA

A longstanding industry complaint with the FDA premarket approval process (not limited to generic drugs, by any means) is the so-called "moving target," in which product sponsors satisfy what they believe were the applicable requirements, only to be told that the requirements have changed or that additional requirements are now applicable. In an effort to address this longstanding concern, FDAMA amended the FDC Act in 1997 to provide for a binding presubmission conference for both NDAs and ANDAs. Assuming written agreement is reached, the agreement is not to be changed after testing begins, except with the sponsor's consent or based on an FDA determination that a new, substantial scientific issue essential to the safety or effectiveness of the drug has been identified.† In practice, the provision has been of limited use. With regard to ANDAs, it applies only to agreements on the design and size of bioavailability and bioequivalence studies. Even within that limited scope, few prospective ANDA sponsors have reached written agreements with the FDA regarding study design.

Disagreements with the FDA staff over scientific or technical issues can be appealed up through the chain of command.‡ At least in theory, appeals could continue up to the FDA Commissioner. If a disputed scientific or technical issue regarding a pending ANDA or 505(b)(2) NDA cannot be resolved through the appeals process, judicial review is usually not a realistic option. Before seeking judicial review, a drug sponsor generally must utilize the administrative process for challenging FDA's decision that its application will not be approved. This procedure calls for a formal evidentiary hearing before FDA's Administrative Law Judge (ALJ), an initial decision by the ALJ, and a final agency decision by the FDA Commissioner or his or her delegate. Only then is judicial review available.§ Unfortunately for industry, this administrative process is unlikely to result in a satisfactory decision on the merits for the drug sponsor. Moreover, it is very time consuming and is likely to take a number of years to run its course. Thus, as a practical matter, it has very seldom been used by industry. In some cases, it may be possible to characterize an ANDA or 505(b)(2) NDA dispute in "legal" terms, thereby increasing the chance of obtaining judicial review without first resorting to the administrative hearing process.

Finally, in some cases, ANDA and 505(b)(2) NDA sponsors will discover that they have relied on agency advice that is subsequently repudiated. In general, such

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* *Somerset Pharmaceuticals*, *supra*, n. ‡‡, p. 351.

† 21 USC § 355(b)(5) and (j)(3).

‡ 21 USC § 360bbb-1; 21 CFR § 10.75.

§ 21 USC § 355(j)(5)(E), (c)(1)(B), and (h).

an innocent applicant will have to bear the brunt of FDA's error.* Judicial relief is generally not available.†

Application Approval Delays

Although Hatch–Waxman Amendments provide that the FDA will approve or disapprove a 505(b)(2) NDA or ANDA within 180 days,‡ the median ANDA approval time is, as of this writing, more than 30 months. One early court challenge to compel the FDA to review a sponsor's ANDAs in timely fashion was rejected.§ However, in another case, a district court ordered the FDA to render a decision (either approve or refuse to approve) a 505(b)(2) NDA.¶ The FDA initially appealed but subsequently withdrew its appeal and approved the application. This decision probably should be viewed as one involving unique facts, including the passage of a substantial length of time during which the FDA had failed to take any action on the pending application and FDA's letter to the sponsor in which the agency indicated that the review was complete but the agency could not, in essence, make up its mind.

Much of the delay in reviewing and approving ANDAs can be attributed to the successful Prescription Drug User Fee Act (PDUFA), which requires drug sponsors to pay user fees in connection with NDAs for prescription drugs. The user fee legislation includes a commitment by the FDA that it will review and take action on 90% of all complete original applications and supplements within 10 months of receipt. The user fee legislation has had the practical effect of diverting agency resources that would otherwise have been used for the review of ANDAs to the innovator product side of the FDA's Center for Drug Evaluation and Research.

Many in the generic drug industry believe that generic drug user fees would help alleviate the delay in reviewing and approving ANDAs. The FDA has charged user fees for innovator drug NDAs (including 505(b)(2) NDAs) since 1992 and more recently for medical device premarket approvals and 510(k) ("substantial equivalence") determinations, innovator animal drug applications, and generic animal drug applications. Different segments of the generic drug industry have debated the wisdom of generic drug user fees for over a dozen years. As of the time of this writing, it appears that legislation will be enacted to establish generic drug user fees starting with fiscal year 2013 (beginning October 1, 2012). As with PDUFA, this legislation would include FDA commitments to meet performance goals. Legislation would also address the backlog of pending ANDAs and supplements.

The FDA's Office of Generic Drugs has a medical affairs staff that is able to address some—but no means all—"medical" issues that sometimes arise in connection with ANDAs. Examples of such ANDAs include modified-release products with complex bioequivalency issues and nonsystemically absorbed drug products where a

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* See, e.g., FDA May 25, 2011 letter at 17–18, *supra*, n. *, p. 353 (involving subsequently repudiated FDA advice recommending a 505(b)(2) NDA, rather than an ANDA, for a generic colchicine drug product).

† *Purepac Pharmaceutical Company*, *supra*, n. **, p. 340 (involving erroneous FDA advice on how to address an Orange Book patent).

‡ 21 USC § 355(j)(5)(A) and (c)(1).

§ *In re Barr Laboratories, Inc.*, 930 F.2d. 72 (D.C. Cir. 1991).

¶ *Sandoz, Inc. v. Leavitt*, 427 F. Supp.2d 29 (D.D.C. 2006) (involving somatropin).

small clinical trial is used to assess bioequivalency. If these issues cannot be resolved within the Office of Generic Drugs, a "consult" opinion from the corresponding new drug review division is necessary. These "consults" are typically assigned a low priority by the new drug review division because they do not count against FDA's user fee deadlines and quotas. Waiting for a "consult" opinion can result in a delay in ANDA review and approval. Thus, in appropriate situations, a 505(b)(2) NDA may be preferable to an ANDA, as the 505(b)(2) application will get the benefit of the user fee time commitments.

Therapeutic Equivalence

Senior FDA officials have long been on record as stating that there is no evidence that an FDA-approved generic product cannot be safely and effectively substituted for its brand-name counterpart. Nevertheless, concerns have arisen at different times and in different contexts. Recently, publicized concerns have been raised by clinicians regarding apparent clinical differences between some FDA-approved generic products and their brand-name counterparts, particularly in the area of mental health and antiseizure drugs.

Under state pharmacy laws, a pharmacist may (or must) substitute a generic version of an innovator product when the physician prescribes the innovator product by brand name, unless the physician or patient objects to substitution. The substitution provisions of most state pharmacy laws cover all ANDA products that have been approved by the FDA as therapeutically equivalent to their brand-name counterparts. However, in a small number of states, state formulary boards may conduct their own review of the information and data submitted to the FDA to support an ANDA approval and may make their own decisions on product substitutability within that state. These states that engage in making their own drug substitution decisions provide another opportunity for innovator drug sponsors to block substitution. Most recently, these efforts have focused on mental health drugs. Prior efforts focused on so-called "narrow therapeutic index" drugs.

Risk Evaluation and Mitigation Strategies

The FDAAA codified a number of existing FDA practices, and granted FDA new authorities, in the areas of postapproval safety and surveillance, a major component of which is known as REMS.* In general, REMS may include labeling, communication strategies with healthcare providers, and limited distribution systems such as limiting distribution to specially certified pharmacies and practitioners.

In general, an ANDA that is approved for an innovator drug subject to REMS will have to mimic the innovator's REMS. Special challenges are presented if certain aspects of the innovator's REMS plan, such as a patient registry and a limited distribution systems, are trade secrets or are patented. If possible, all generic firms are to use a "single, shared system" with the innovator firm. However, the FDA may waive the requirement for a single, shared system if a generic firm is unable to obtain

* 21 USC § 355-1 (as added by FDAAA).

a license for use of the innovator's system. The FDA is expressly authorized (but not required) to "negotiate a voluntary agreement" for the use of the shared system.* It remains to be seen how this requirement will affect the approval and availability of generic versions of drugs subject to special distribution requirements.

Copyrighted Labeling

One innovator drug manufacturer attempted to block generic competition by copyrighting portions of its FDA-approved labeling and then seeking an injunction under federal copyright law against the ANDA sponsor on the basis that its copyright was being infringed. The court ultimately rejected this argument, concluding that the Hatch–Waxman requirement for the "same" labeling takes precedence over copyright law. However, that court recognized that use of the copyrighted materials in a context other than labeling (such as advertising) could well constitute copyright infringement.†

Antitrust Considerations

Agreements between competitors or potential competitors that have the effect of restricting competition may run afoul of federal and state antitrust laws and similar laws. Although a discussion of this area is beyond the scope of this chapter, it is worth mentioning that any generic company would be well advised to consult with antitrust counsel with expertise in pharmaceutical settlements as it develops its business and patent litigation plans.

The MMA requires that certain agreements (including oral agreements) affecting ANDAs (but not 505(b)(2) NDAs) be reported to the FTC and the Antitrust Division of the Department of Justice within 10 business days after they are executed. Specifically, the reporting requirement concerns agreements between the sponsor of a Paragraph IV ANDA and the brand-name drug company regarding the manufacture, marketing, or sale of either the brand-name drug or the ANDA drug or regarding the 180-day exclusivity period. Agreements between two Paragraph IV ANDA sponsors regarding the 180-day exclusivity period must also be reported. Purchase orders for raw materials, equipment and facility contracts, employment or consulting contracts, and packaging and labeling contracts are exempt from the reporting requirement. Information reported to the government is exempt from public disclosure under the Freedom of Information Act (FOIA). The failure to report in timely fashion can result in a civil penalty.‡ The FTC issues an annual report regarding all agreements filed with that agency.§

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* 21 USC § 355-1(i) (as added by FDAAA).

† *SmithKline Beecham Consumer Health Care, L.P. v. Watson Pharmaceuticals, Inc.*, 211 F.3d 21 (2d Cir. 2000) (involving nicotine gum).

‡ MMA, §§ 1111–1115.

§ The FTC FY 2011 report is available at http://www.ftc.gov/os/2011/10/1110mmaagree.pdf. Accessed June 13, 2013.

Freedom of Information Act

Under a longstanding FDA regulation, a summary of the safety and effectiveness data and information that support a drug approval is "immediately" available for public disclosure after NDA approval, with very limited exceptions.* These documents are often very useful to sponsors and prospective sponsors of ANDAs and 505(b)(2) NDAs. In practice, however, the public availability of a data summary, often referred to as an "SBA" or a "summary basis of approval," varies widely.

The FDAAA amended the FDC Act to address this situation.† The FDA is now required to post the "action package" (including labeling, a review summary, and the "decision document") for approval of a NDA drug or a biological on its website within 30 days after approval if the approval involves a new active ingredient and within 30 days after the third FOIA request for the documents for any other NDA drug or biological. In addition, the FDA is required to post on its Internet site a "summary review" within 48 hours after approval, unless the FDA needs additional time for the redaction of nondisclosable information. Although 505(b)(2) NDAs are within the scope of the new provision, the new provision does not affect the public availability of information regarding the approval of ANDAs.

Clinical Trials Registry

In 2007, the FDAAA amended the Public Health Service Act to add requirements for registering "clinical trials," other than Phase I trials, with the National Institutes of Health (NIH).‡ In relevant part, notice of covered clinical studies must be submitted to the NIH for listing on an NIH website. At the time of ANDA or 505(b)(2) NDA submission, a certification regarding compliance with the clinical trials registry requirements (Form FDA 3674) must be submitted.§

The scope of the registry requirement is arguably ambiguous. In light of this uncertainty, the generic industry asserted that the inclusion of in vivo bioequivalency studies within the scope of the reporting requirement was never intended by Congress and that the public availability of this information would adversely affect the business practices of most generic drug firms. Possibly in response to these views, the FDA posted a draft "definitions" document on the NIH website that takes the position that typical ANDA biostudies that measure drug levels in blood or other bodily fluids are outside the scope of the registry and certification requirements; however, a comparative clinical trial used to measure bioequivalence is subject to the new requirements.¶

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* 21 CFR § 314.430(e)(2).

† 21 USC § 355(l) (as amended by FDAAA).

‡ 42 USC § 282(j) (added by FDAAA).

§ *Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff, Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act*, January 2009. Available at http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0224-GDL.pdf. Accessed June 13, 2013.

¶ http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf. Accessed June 13, 2013.

Compliance Issues

In General

Regulatory compliance issues may pose a hurdle to approval of an original ANDA or 505(b)(2) NDA and to approval of supplements to an approved ANDA or 505(b)(2) NDA seeking permission to change the formulation or manufacturing process or make other product improvements. These issues may also threaten the continued manufacture and distribution of an approved drug product. These issues generally first come to light during FDA inspections. The FDA may conduct inspections as part of its statutory obligation to inspect all drug manufacturers once every 2 years,* the Agency's investigation of complaints or other reports about product failures, or preapproval inspections.

If an FDA investigator observes what he or she views as significant problems, particularly in the area of current good manufacturing practices (cGMPs), the investigator is likely to leave a Form FDA-483 listing "Inspectional Observations" at the close of the inspection. Depending on the seriousness of the perceived deviations, the FDA may send the inspected firm a Warning Letter, which is a cease-and-desist letter.

If a drug manufacturer fails to resolve alleged violations that are addressed in the Warning Letter, and particularly if the alleged violations continue over a series of inspections, federal court legal action may result. By going to federal court, where FDA is represented by the US Department of Justice, the government can seek to seize and "condemn" violative products, enjoin a firm and it employees from continued violations of the law, or impose criminal sanctions against a firm and its management.†

The approvability of an ANDA or 505(b)(2) NDA or supplemental ANDA or 505(b)(2) NDA may be affected not only by the compliance status of the sponsor's own facilities but also by the regulatory status of active pharmaceutical ingredient suppliers, clinical research organizations, testing laboratories, and other firms referenced in the ANDA or 505(b)(2) NDA that have a role in the development and production of the generic drug product. This situation is complicated by the fact that, under typical commercial arrangements, the ANDA or 505(b)(2) NDA sponsor has no direct access to its suppliers' internal procedures and similar documents, which are typically made available to FDA in the form of a drug master file that the ANDA or 505(b)(2) NDA sponsor has the right to reference but not actually review. Similarly, correspondence between the FDA and a supplier may not be available to the ANDA or 505(b)(2) NDA sponsor. Thus, the ANDA or 505(b)(2) NDA sponsor may be at the mercy of others, without having any ability to resolve the compliance issues, or even find out about them. An ANDA or 505(b)(2) NDA sponsor should seek to address this area in contracts with its suppliers.

Recalls

Problems uncovered during FDA inspections, as well as problems discovered by a manufacturer itself or by others, can lead to product recalls. In general, the FDA

* 21 USC § 360(h).

† 21 USC § 334, § 332, and § 333, respectively.

has no legal authority to compel a firm to conduct a recall of a drug product; thus, drug recalls are nominally "voluntary." As a practical matter, however, firms often have no alternative but to conduct a recall of product that violates legal and regulatory requirements in some manner. The factors that support a decision to conduct a "voluntary" recall include FDA's ability to issue adverse publicity about the firm, the threat of legal action, and mitigation of product liability exposure. The FDA has issued recall "guidelines" and strongly prefers that firms conducting a recall follow the guidelines.*

Although a discussion of the conduct of a recall is beyond the scope of this book, it should be noted that every drug manufacturer should have contingency plans for conducting a recall. If properly handled, the impact of a recall can be minimized. A firm's recall plan should address assessing the health hazard associated with a product problem; contacting regulatory authorities; contacting customers; public relations; handling physician, pharmacist, and consumer inquiries; and collecting and handling returned product. Of course, in any particular situation, some of these steps may not be necessary depending on the nature of the product and a firm's operations. A firm that does not have the requisite in-house expertise should seek the assistance of qualified outside help in this area, preferably before the need arises.

Recalls are commonplace and affect all drug firms ranging from multinational innovator companies to small niche generic firms. In a typical year, approximately 500 recalls of drug products are reported by the FDA. The great majority of these recalls involve the failure of a product to comply with its specifications in some manner, such as dissolution problems or subpotency near the end of the product's shelf life. For the most part, these recalls present technical violations that present either no or minor public health issues.

"Fraud Policy"; cGMP Problems

In response to widespread problems involving the submission and review of ANDAs in the late 1980s and early 1990s, the FDA adopted its application integrity policy, commonly known as the "fraud policy," in 1991.† The fraud policy is triggered if the FDA concludes that the sponsor of an ANDA or 505(b)(2) NDA (or other premarket approval application) has committed fraud, bribery, illegal gratuities, or other unlawful acts that call into question the integrity of data supporting the sponsor's application. The policy can also be triggered by a pattern of material errors due to sloppiness and similar causes.

If the FDA notifies a firm that the fraud policy is applicable, the FDA will stop reviewing the firm's applications and supplements until the firm has rehabilitated itself. Until rehabilitation has been completed, the firm may also find itself ineligible for government contracting. Rehabilitation consists of removal of all individuals who were associated with the improper acts followed by a "validity assessment" to determine the reliability of data in the firm's applications. Validity assessments are usually conducted by independent consultants (typically former FDA employees), retained at the firm's expense, followed by FDA spot-checking of data. FDA's

* 21 CFR § 7.40–§ 7.59.

† 56 Fed. Reg. 46,191 (September 10, 1991).

decision to invoke the fraud policy with respect to an ANDA or 505(b)(2) NDA sponsor, or even a contract manufacturer with a significant role in preparation of an ANDA or 505(b)(2) NDA, could result in delays of one to a number of years in ANDA or 505(b)(2) NDA approval.

Substantial inspectional issues related to apparent cGMP problems may have the same practical effect as the "fraud policy." The FDA may decline to approve the firm's applications and supplements until all cGMP issues have been resolved and the firm has been "rehabilitated," often using the same process used when the "fraud policy" has been invoked.

Debarment

In response to irregularities in the generic drug industry, the FDC Act was amended in 1992 to include debarment provisions.* Both individuals and business entities can be debarred if convicted of certain crimes associated with a lack of trustworthiness (e.g., fraud, perjury, and obstruction of justice); a high managerial agent can also be debarred if he or she had knowledge of such activity and failed to take remedial action. All drug applications are required to include a certification that the sponsor did not use and will not use in any capacity the services of a debarred person in connection with the application. Thus, ANDA and 505(b)(2) NDA sponsors have an obligation to ensure that they do not employ debarred individuals and do not use, directly or indirectly, the services of an individual or business entity that has been debarred.†

CONCLUSION

In addition to the technical hurdles that a prospective generic drug sponsor must overcome, there are a number of obstacles that many would characterize as being of a legal nature. Uncertainties about how the FDA is implementing and interpreting some statutory provisions, such as 180-day generic drug exclusivity, along with the possibility of litigation, complicate business planning in many cases. A prospective ANDA or 505(b)(2) NDA sponsor facing a situation that could pose hurdles of this type would be well advised to seek appropriate regulatory and legal advice.

* 21 USC § 335a.

† FDA's debarment list is available at www.fda.gov/ora/compliance_ref/debar/default.htm. Accessed June 13, 2013. To date, over 100 individuals have been debarred, the great majority of them permanently.

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GENERIC DRUG PRODUCT DEVELOPMENT

Solid Oral Dosage Forms

Second Edition

In this era of increased pharmaceutical industry competition, success for generic drug companies is dependent on their ability to manufacture therapeutic-equivalent drug products in an economical and timely manner, while also being cognizant of patent infringement and other legal and regulatory concerns.

Generic Drug Product Development: Solid Oral Dosage Forms, Second Edition presents in-depth discussions from more than 30 noted specialists describing the development of generic drug products—from the raw materials to the development of a therapeutic-equivalent drug product to regulatory approval.

Major topics discussed include

- Active pharmaceutical ingredients
- Experimental formulation development, including a new section on Quality by Design (QbD)
- Scale-up
- Commercial product formulation
- Quality control and bioequivalence
- Drug product performance
- ANDA regulatory process
- Post-approval changes
- Post-marketing surveillance
- Legislative and patent challenges

This second edition also contains a new chapter on the relationship between the FDA and the United States Pharmacopeia and in Chapter 4, using specific examples, the application of Quality by Design (QbD) during formulation development is examined. The book is a thorough guide to the development of solid oral generic dosage formulations. This textbook is ideal for the pharmaceutical industry, graduate programs in pharmaceutical sciences, and health professionals working in the area of generic drug development.

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